(19) Europäisch s Patentamt
European Patent Offic
Office europé n des br vets

(11) Publication number : **0 554 107 A1**

(12) EUROPEAN PATENT APPLICATION

(21) Application number : **93300661.1**

(22) Date of filing : **29.01.93**

(51) Int. Cl.[5] : **C07D 249/12**, C07D 403/12, A61K 31/41

(30) Priority : **30.01.92 US 828394**

(43) Date of publication of application : **04.08.93 Bulletin 93/31**

(84) Designated Contracting States : **AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

(71) Applicant : **ORTHO PHARMACEUTICAL CORPORATION**
U.S. Route 202 P.O. Box 300
Raritan New Jersey 08869-0602 (US)

(72) Inventor : **Bandurco, Victor T.**
204 Love Road
Bridgewater, NJ 08807 (US)
Inventor : **Wachter, Michael P.**
52 North Street
Bloomsbury, NJ 08804 (US)
Inventor : **Murray, William V.**
447 Township Line Road
Belle Mead, NJ 08502 (US)
Inventor : **Schwender, Charles F.**
Box 597-C, Philhower Road
Califon, NJ 07830 (US)

(74) Representative : **Mercer, Christopher Paul et al**
Carpmaels & Ransford 43, Bloomsbury Square
London WC1A 2RA (GB)

(54) Substituted triazoles as angiotensin II inhibitors.

(57) This invention relates to novel bis-biphenyl substituted 3-mercapto-1,2,4-tetrazoles and to pharmaceutically acceptable salts thereof.

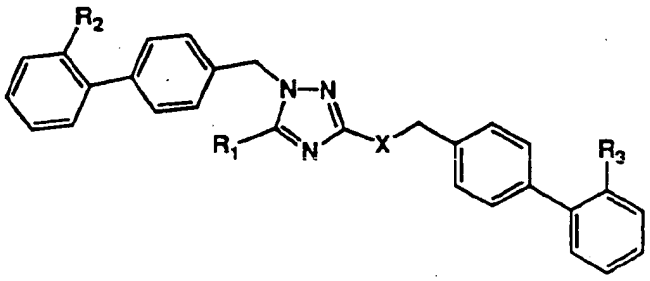
The compounds are angiotensin II receptor antagonists, and are useful in treating hypertension (lowering high blood pressure), congestive heart failure, elevated ocular pressure, cerebral stroke, angina, cardiac insufficiency, myocardial infarction or diabetic nephropathy.

The invention also relates to a pharmaceutical composition comprising a compound of the invention, a method of treating a physiological condition in a mammal that is mediated by angiotensin 11 which comprises administering to the mammal an effective amount of a compound of the invention, and novel processes for preparing the compounds of the invention.

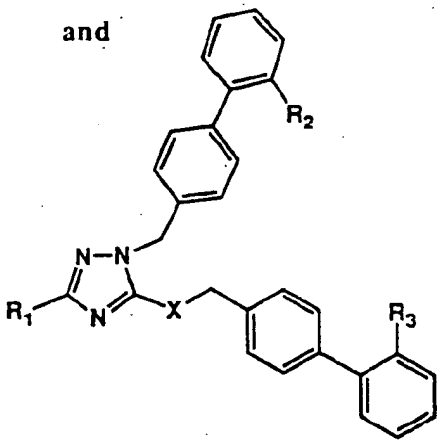
EP 0 554 107 A1

Field of th Invention

This inv ntion relates to novel compounds of th following formulae:



and



The invention also relates to pharmaceutical compositions comprising a compound of the invention as the active ingredient, a method of treating a physiological condition in mammals that is mediated by angiotensin II by administration of a compound of this invention, to novel processes for preparing the compounds of the invention and to pharmaceutically acceptable salts thereof.

The novel compounds are angiotensin II receptor antagonists and are useful in treating hypertension (lowering of high blood pressure), congestive heart failure, elevated ocular pressure, cerebral stroke, angina, cardiac insufficiency, myocardial infarction and diabetic nephropathy.

Background of the Invention

The role of hypertension in cardiac dysfunction is continually evolving. Therefore, the treatment of hypertension continues to be clinically important. The discovery of new agents with fewer undesirable side effects is a therapeutic target since hypertension must be treated chronically. Long term toxicity as well as long term patient compliance are important considerations in the development of new antihypertensive agents.

One of the blood pressure regulating systems in man is the renin-angiotensin system. The renin-angiotensin system produces angiotensinogen in the kidney which is converted by renin to angiotensin I. The non-vasoconstricting peptide angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent vasoconstrictor. The discovery of nonpeptide angiotensin converting enzyme (ACE) inhibitors represented an important new step in the treatment of hypertension and several of these inhibitors, such as captopril and enalapril, are widely accepted. Progress toward renin inhibitors as therapeutic agents, however, has been far less successful.

Direct antagonism of angiotensin II binding at the receptor is an attractive goal because it is the actual vasoconstricting event in this pathway. By inhibiting the receptor, one would expect to have few r side effects than by inhibiting earlier st ps in the pathway. Also, by acting at the receptor, as. opposed to on of the enzymes, large deposits of angiotensinogen and angiotensin I should not build up. In some systems, this build up can give rise to shunting mechanisms which can lead to other sid effects.

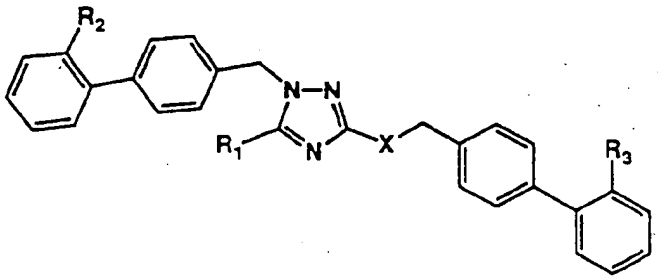
Duncia et al. [J. Med. Chem., (1990), 33, 1312] Carini et al. [J. Med. Chem. (1990), 33, 1330], Johnson et

al. [Drug News and Perspectives, (1990), 3, (6), 337], Chang et al. (EP 041,594 A) and Roberts et al. (G.B. 18402) all describe compounds which are inhibitors of angiotensin II.

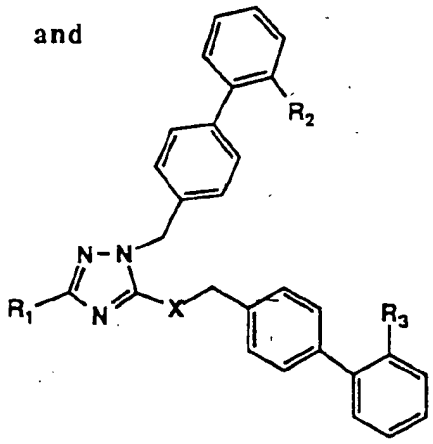
A number of 3-thio-1,2,4-triazoles have been describ d in the literatur [Beyer, H. et al., Ber. (1960) 637, 135; Kroger, C. t al., Ber (1961) 643, 121; and Kroger, C. et al., Ber. (1961) 643, 128; CA99 (21): 175676W; CA 102(25): 216901S; CA 84(5): 29998b; CA83(26): 20942u. None of thes compounds, however, is dibenzylated. The compounds of the present invention are bis-biphenyl or phenylphthalamate substituted 3-mercapto-1,2,4-triazoles.

Detailed Description of the Invention

The invention relates to bis-biphenyl substituted 3-thio-1,2,4-triazoles of the formula:



and



Wherein R_1 is selected from H, C_{1-10} alkyl, C_{2-10} alkenyl, benzyl, substituted benzyl wherein the substituent is selected from C_{1-5} alkyl, NO_2 and halo such as chloro, bromo, fluoro or iodo; phenyl, phenylalkenyl such as 2-phenylethene or 2-phenylpropylene and substituted phenyl wherein the substituent is selected from C_{1-5} alkyl, NO_2, C_{1-8} alkoxy and halo such as chloro, bromo, fluoro or iodo;

R_2 and R_3 are the same or different and are selected from CO_2H, CO_2C_{1-5} alkyl, CN, $CONH_2$, $CON(R_4)_2$ wherein R_4 is C_{1-6} alkyl; 5-tetrazolo, CONHOH and $CONR_4OH$, wherein R_4 is C_{1-6} alkyl, $CONHR_4$ wherein R_4 is 5-tetrazolo:

and X is selected from S, SO and SO_2.

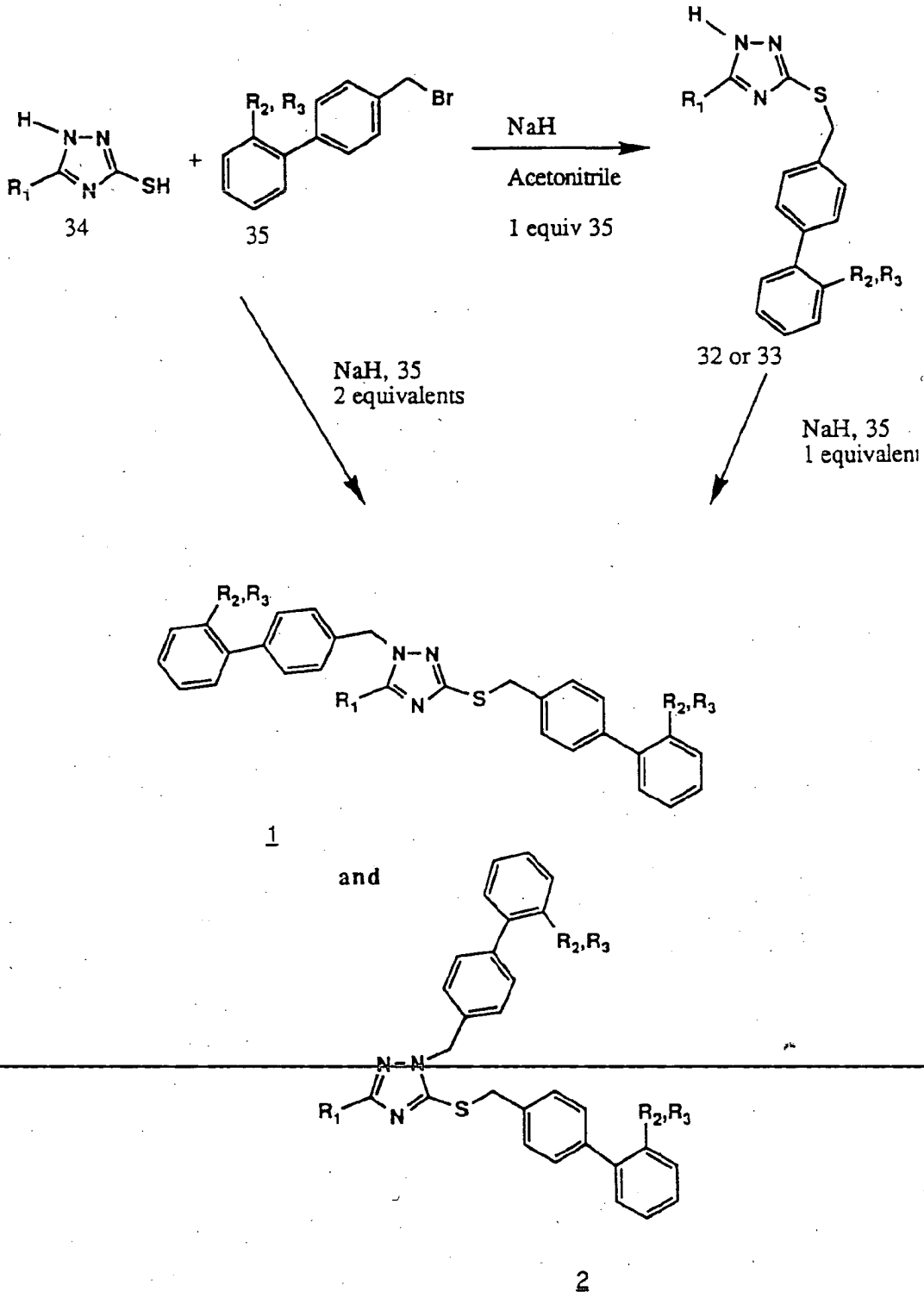
The preferred compounds of the invention are those compounds wherein R_1 is C_{1-10} alkyl; R_2 is COOH or 5-tetrazolo and R_3 is CO_2H, CN or CO_2C_{1-6} alkyl.

The preferred species of the invention are the following compounds:

Disodium 5-butyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole; 5-pentyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole; 3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole. 3-[4-(2'-cyanoph nyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolo-phenyl)benzyl]-1,2,4-triazole; and 1-[(2'-carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-heptyl-1,2,4-triazole.

The invention also relates to a novel process for preparing the novel compounds as disclosed in Scheme1.

Scheme 1



As can be seen from Schem 1 thos compounds wherein X is S ar prepared by first reacting a substituted mercaptotriazole with a substitut d biphenylylhalide in a suitable solv nt such as, for example, acetonitrile, dimethyformamide and alcohols such as methanol, in the presence of a base such as, for xample, sodium hydride, sodium hydroxide, potassium hydroxide, potassium hydride and potassium carbonate. The reaction mix-

ture is stirred for from about 1-16 hours after which the solvent is removed in vacuo or by other means known to those skilled in the art. The residue is dissolved in an appropriate solvent such as, for example, ether, ethyl acetate or methylene chloride or tetrahydrofuran, and the solution is washed with dilute acid such as, for example, dilute hydrochloric acid, and then washed with water or brine. The solvent is dried and the product is collected by methods known to those skilled in the art; for example, the solution can be crystallized or chromotographed over an adsorbent material such as, for example, silica gel and the product eluted with a suitable solvent. The product obtained is then reacted with a second equivalent of the base and the biphenylylhalide to obtain the substituted triazoles. If in the reaction scheme, two equivalents of the base and the biphenylylhalide are employed, the substituted triazoles are obtained directly and separated and purified by methods known to those skilled in the art.

Those compounds wherein R_2 or R_3 is $CONH_2$ $CON(R_4)_2$, $CONHR_4$, CONHOH or $CONR_4OH$ are prepared by: (1) converting structure 1 or 2 to an appropriate acid chloride as essentially described by W. Murray et al., in Synthesis (1), 18 (1991) using oxalyl chloride or thionyl chloride in a solvent such as methylene chloride or THF. The acid chloride formed is then added to a solution of the amine such as $HN(C_{1-6}$ alkyl$)_2$, $NH_2(C_{1-6}$ alkyl), benzylamine, 5-aminotetrazole or amine hydrochloride such as $NH_2OH{\cdot}HCl$, $NH(C_{1-6}$ alkyl$)OH$ in an appropriate solvent such as methylene chloride or THF and a base such as triethylamine or pyridine. The amide will generally precipitate out of solution. Hydroxamides wherein R_2 or R_3 is CONHOH or $CONR_4OH$ are isolated by washing with water or dilute acid such as dilute hydrochloric acid, separation of layers, and concentration under reduced pressure.

The pharmaceutically acceptable salts of the invention include the sodium, potassium and pyridinium salts which are prepared by methods known to those skilled in the art.

The compounds of the invention where X is SO or SO_2 are prepared by dissolving a compound of structure 1 or 2 in an appropriate solvent such as methylene chloride or tetrachloroethylene. The solution is cooled to between 0 and 10°C and a solvent such as methylene chloride or tetrachloroethylene is added dropwise. To generate the sulfoxide (X=SO) 1 equivalent of metachloroperbenzoic acid in an appropriate solvent (MCPBA) is used. To generate the sulfone (SO_2) two or more equivalents of MCPBA are used. Once the addition is complete the mixture is stirred for between 0 and 6 hours at between 0 and 25°C. Dilute base such as 10% NaOH or 5% KOH is added and the layers are separated. The organic layer is then washed with brine or water, dried over an appropriate drying agent, such as sodium sulfate or magnesium sulfate, filtered and concentrated in vacuo. The residue is then crystallized from an appropriate solvent such as ethyl acetate or ether, or a solvent pair such as ethyl acetate/ hexane or ether/ hexane to afford the pure compound.

The biphenylylbromides **35** were prepared by the method of Duncia , et al. J. Org. Chem. 1991, 56, 2395-2400 or Aldrich et al US patents 4,870,186 and 4,874,867. The substituted mecaptotriazoles **34** were prepared as described by Von Beyer et al., Leibigs Ann. 637, 135 (1960).

The compounds of this invention are angiotensin II receptor antagonists, and are useful in treating hypertension (lowering high blood pressure), congestive heart failure, elevated ocular pressure, cerebral stroke, angina, cardiac insufficiency, myocardial infarction and/or diabetic nephropathy.

Pharmaceutical compositions comprising a compound of the invention as the active ingredient in intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral. The composition may also be administered by means of an aerosol. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. For example, in the case of oral liquid preparations (such as suspensions, elixirs and solution), water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. In the case of oral solid preparations (such as, for example, powders, capsules and tablets), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, may be used. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are preferably employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, to aid solubility or for preservative purposes, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions will generally be in the form of a dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, containing from 0.1 to about 1000 mg/kg, and preferably from about 1 to 200 mg/kg of the active ingredient.

The following experimental examples describe the invention in greater particularity and are intended to be a way of illustrating but not limiting the invention.

In the Examples

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The infrared spectra (IR) were recorded on a Beckman Instruments IR-B spectrophotometer and are expressed in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a GE QE 300, a Bruker AC 300 or an IBM WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. EI and CI mass spectra were obtained on a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer.

EXAMPLE 1

5-Pentyl-3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **32**

A mixture of 3-mercapto-5-pentyl-1,2,4-triazole (3.42g, 0.02 mole), sodium hydride 80% in oil (1.0g, 0.033 mole) and 4-(2'-carbomethoxyphenyl)benzylbromide (6.1g, 0.02 mole) was stirred for 6h in acetonitrile (300 mL). The resultant mixture was then filtered through celite, and rotovapped to a brown residue. The residue was chromatographed on silica gel using hexane / 40% ethyl acetate as the mobile phase. Concentration of the eluates afforded 6.5g (82%) of the title compound as a low melting, white, waxy solid. ^{1}HNMR ($CDCl_3$) 7.82 (1H, d, J = 7 Hz); 7.60 - 7.20 (7H, m); 4.38 (2H, s); 3.63 (3H, s); 2.78 (2H, t, J = 7 Hz); 1.70 (2H, m); 1.4 (4H, m); 1.31 (3H, t, J = 4 Hz). Mass Spec (DCI) m/z 396 (M+H). Analysis calc'd for $C_{22}H_{25}N_3O_2S$: C,66.82; H,6.32; N,10.00. found: C,66.67; H,6.34; N,10.00.

EXAMPLE 2

5-Pentyl-3-[4-(2'-cyanophenyl)benzyl]mercapto-1,2,4-triazole **33**

The title compound was prepared following the procedure of Example 1 using 4-(2-cyanophenyl)benzylbromide as the biphenylylbromide, Yield 88%, mp 105-106°C. Mass Spec (DCI) m/z 363 (M+H). Analysis calc'd for $C_{21}H_{22}N_4S$: C,69.56; H,6.12; N,15.46. found: C,69.59; H,5.91; N,15.34.

EXAMPLE 3

5-Pentyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **21** and 5-Pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **5**.

A) A mixture of 5-pentyl-3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole (3.95g, 0.01 mole), sodium hydride 80% (0.5g, 0.01 mole) and 4-(2-carbomethoxyphenyl)benzylbromide (3.04g, 0.01 mole) were combined in 350 mL of acetonitrile.and the mixture was refluxed for 5h. The resulting mixture was filtered through celite and rotovapped to a brown residue. The residue was chromatographed on silica gel using hexane / 30% ethyl acetate as the mobile phase. Concentration of the eluates afforded 5-pentyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **21** as a colorless oil (1.36g, 22%) and 5-pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **5** as a colorless oil (2.52g, 41%).

B) A mixture of 3-mercapto-5-pentyl-1,2,4-triazole (1.71 g, 0.01 mole), sodium hydride, 80% in oil (1.0g, 0.033 mole) and 4-(2'-carbomethoxyphenyl)benzylbromide (6.1 g, 0.02 mole) was refluxed for 8h in acetonitrile (300 mL). The resultant mixture was then filtered through celite,and rotovapped to a brown residue. The residue was chromatographed on silica gel using hexane / 30% ethyl acetate as the mobile phase. Concentration of the eluates afforded 5-pentyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **21** (0.9g, 15%) and 5-pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **5** (1.02g, 16%) as colorless oils.

Compound 21: ^{1}NMR ($CDCl_3$) 7.82 (2H, m); 7.6 - 7.2 (14H, m); 5.16 (2H, s); 4.51 (2H, s); 3.63 (3H, s); 3.60 (3H, s); 2.76 (2H, t, J = 7 Hz); 1.78 (2H, m); 1.40 (4H, m); 1.31 (3H, m). Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{37}N_3O_4S \cdot 1/2\ H_2O$: C,70.68; H,6.09; N,6.68. found: C,70.47; H,5.59; N,6.90.

Compound 5: ^{1}HNMR ($CDCl_3$) 7.82 (2H, m); 7.6-7.15 (14H, m); 5.24 (2H, s); 4.41 (2H, s); 3.62 (3H, s); 3.60 (3H, s); 2.67 (2H, t, J = 7 Hz); 1.65 (2H, m); 1.35 (4H, m); 0.85 (3H, t, J = 4 Hz). NOE enhancement of 2.67 t when 5.24 s irradiated. Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{37}N_3O_4S \cdot H_2O$: C,69.69; H,6.16; N,6.59. found: C,69.32; H,6.00; N,6.86.

EXAMPLE 4

5-Butyl-2,3-bis-[4-(2'-carbomethoxyphenyl)b nzyl]mercapto-1,2,4-triazol **17**

5-Butyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **1**

The title compounds were prepared by following the procedure of Example 3.

Compound 17: Mass Spec (DCI) m/z 606 (M+H). Analysis calc'd for $C_{36}H_{35}N_3O_4S \cdot 1/2\ H_2O$: C,70.34; H,5.90; N,6.83. found: C, 70.60; H,6.06; N,7.12.

Compound 1: Mass Spec (DCI) m/z 606 (M+H). Analysis calc'd for $C_{36}H_{35}N_3O_4S$: C,71.39; H,5.82; N,6.94. found: C,70.90; H, 5.22; n,7.16.

EXAMPLE 5

5-Isobutyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **19**

5-Isobutyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **3**

The title compounds were prepared by following the procedure (B) of Example 3.

Compound 19: Mass Spec (DCI) m/z 606 (M+H)

Compound 3: Mass Spec (DCI) m/z 606 (M+H). Analysis calc'd for $C_{36}H_{35}N_3O_4S \cdot 1/2\ H_2O$: C,70.34; H,5.90; N,6.83. found: C,70.30; H,5.66; N,7.12.

EXAMPLE 6

5-Hexyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **24**

5-Hexyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **8**

The title compounds were prepared by following the procedure (B) of Example 3.

Compound 24: Mass Spec (DCI) m/z 634 (M+H)

Compound 8: Mass Spec (DCI) m/z 634 (M+H). Analysis calc'd for $C_{39}H_{39}N_3O_4S \cdot 1/2\ H_2O$: C,71.00; H,6.27; N,6.53. found: C,70.96; H,6.47; N,6.81.

EXAMPLE 7

5-Heptyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **25**

5-Heptyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **9**

The title compounds were prepared by following the procedure (B) of Example 3.

Compound 9: Mass Spec (DCI) m/z 648 (M+H). Analysis calc'd for $C_{39}H_{41}N_3O_4S \cdot 1/2\ H_2O$: C,71.32; H,6.44; N,6.40. found: C,71.31; H,6.38; 6.96.

Compound 25: Mass Spec (DCI) m/z 648 (M+H). Analysis calc'd for $C_{39}H_{41}\ N_3O_4S \cdot 1/2\ H_2O$: C,71.32; H,6.44; N,6.40. found: C,71.25; H, 6.73; N,6.63.

EXAMPLE 8

3-[(2'-Cyanophenyl)benzyl]mercapto]-2-(2'-carbomethoxyphenyl)benzyl-5-butyl-1,2,4-triazole **28**

3-[(2'-Cyanophenyl)benzyl]mercapto]-1-(2'-carbomethoxyphenyl)benzyl-5-butyl-1,2,4-triazole **13**

The title compounds were prepared by following procedure (A) of Example 3 using compound 33 in place of compound 32.

Compound 28: Mass Spec (DCI) m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S \cdot 0.25\ H_2O$: C,72.81; H,5.68; N,9.70. found: C,72.66; H,5.79; N,9.92.

Compound 13: Mass Spec (DCI) m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S \cdot 0.25\ H_2O$: C,72.81; H,5.68; N,9.70. found: C,72.81; H,5.78; N,10.15.

EXAMPLE 9

5-Benzyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **27**

The title compound was prepared by following the procedure (B) of Example 3.
Compound 27: Mass Spec (DCI) m/z 640 (M+H). Analysis calc'd for: C,73.22; H,5.20; N,6.57. found: C,73.16; H,5,25; N,6.10.

EXAMPLE 10

3-[(2'-Cyanophenyl)benzyl]mercapto]-1-(2'-carbomethoxyphenyl)benzyl-5-pentyl-1,2,4-triazole **14**

The title compound was prepared by following the procedure of Example 8.
Compound 14: Mass Spec (DCI) m/z 587 (M+H). Analysis calc'd for $C_{36}H_{34}N_4O_2S$: C,73.69; H,5.84; N,9.55. found: C,73.54; H,5.94; N,9.46.

EXAMPLE 11

5-Pentyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **6**

5-Pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole (1.24g, 0.002 mole) was dissolved in methanol (35mL), 30% KOH (10ml) was added to this solution and the reaction was refluxed for 8h. The resultant mixture was concentrated in vacuo and partitioned between methylene chloride and water (50 mL each). The methylene chloride layer was removed and the aqueous layer was acidified to pH 1 with dilute HCl. The aqueous layer was extracted with 3 portions of methylene chloride (50 mL each), dried over sodium sulfate, filtering and concentrated to a yellow foam (1.0g, (83%). Mass Spec (DCI) m/z 592 (M+H). Analysis calc'd for $C_{35}H_{32}N_3O_4S \cdot 2H_2O$: C,66.97; H,5.63; N,6.69. found: C,67.06; H,5.76; N,6.39.

EXAMPLE 12

5-Pentyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **23**

The title compound was prepared according to the procedure of Example 11. Yield 72 %, mp 116-120 °C. Mass Spec (DCI) m/z 592 (M+H). Analysis calc'd for $C_{35}H_{32}N_3O_4S \cdot H_2O$: C,68.95; H,5.79; N,6.89. found: C,68.80; H,5.41; N,7.12.

EXAMPLE 13

5-Butyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **18**

The title compound was prepared according to the procedure of Example 11. mp 118 - 122 °C. Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{31}N_3O_4S$: C,70.70; H,5.41; N,7.27. found: C,70.17; H,5.00; N,7.29.

EXAMPLE 14

Disodium 5-Butyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **2**

The title compound was prepared according to the procedure of Example 11. The sodium salt was formed by dissolving the triazole in methanol containing 2 equivalents of sodium methoxide and subsequent concentration in vacuo. mp 235°C. Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{29}N_3O_4SNa_2 \cdot 1.25\ H_2O$: C,63.39; H,4.93; N6.50; found: C,63.11; H,4.90; N,6.89.

EXAMPLE 15

Sodium 5-isobutyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **4**

The title compound was prepared according to the procedure of Example 11. The sodium salt was formed by dissolving the triazole in methanol containing 1 equivalent of sodium methoxide and subsequent concen-

tration in vacuo. mp 143 °C (dec.). Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{30}N_3O_4SNa{\cdot}2\ H_2O$: C,64.23; H,5.23: N,6.60; found: C,64.66; H,4.99; N,6.69.

EXAMPLE 16

Sodium 5-isobutyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **20**

The title compound was prepared according to the procedure of Example 11. The sodium salt was formed by dissolving the triazole in methanol containing 1 equivalent of sodium methoxide and subsequent concentration in vacuo. mp 140°C (dec.). Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{30}N_3O_4SNa{\cdot}H_2O$: C,66.10; H,5.38; N,6.80. found: C,65.81; H,5.10; N,6.84.

EXAMPLE 17

5-Heptyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **10**

The title compound was prepared according to the procedure of Example 11. mp 78 - 80°C. Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{37}N_3O_4S{\cdot}2\ H_2O$: C,67.77; H,6.30; N,6.41. found: C,68.09; H,6.17; N,5.98.

EXAMPLE 18

Sodium 5-isobutyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **26**

The title compound was prepared following the procedure of Example 11. The sodium salt was formed by dissolution in methanol containing 1 equivalent of sodium methoxide and subsequent concentration in vacuo. mp 110 °C (dec.). Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{36}N_3O_4SNa \cdot 1.5H_2O$: C,66.45; h,6.02; N,6.28. found: C,66.27; H,5.59; N,6.12.

EXAMPLE 19

5-Benzyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **11**

The title compound was prepared according to the procedure of Example 11. Mass Spec (DCI) m/z 612 (M+H). Analysis calc'd for $C_{37}H_{29}N_3O_4S{\cdot}0.4\ H_2O$: C,71.80; H,4,85; N,6.79. found: C,72.02; H,5.14; N,6.39.

EXAMPLE 20

3-[4-(2'-Cyanophenyl)benzyl]mercapto]-1-[4-(2'-carboxyphenyl)benzyl]-5-pentyl-1,2,4-triazole **12**

5-Pentyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole (1.18g, 0.002 mole) was dissolved in methanol (35mL). 30% KOH (10mL) was added to this solution and the reaction mixture was refluxed for 2h. The resultant mixture was concentrated in vacuo and partitioned between methylene chloride and water (50 mL each). The methylene chloride layer was removed and the aqueous layer was acidified to pH 1 with dilute HCl. The aqueous layer was extracted with 3 portions of methylene chloride (50 mL each), dried over sodium sulfate, filtered and concentrated to a white foam (1.0g, 88% yield). Mass Spec (DCI) m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S{\cdot}0.25\ H_2O$: C,72.83; H,5.68; N,9.71. found: C,72.58; H,5.66; N,9.68.

EXAMPLE 21

1-[(2'-Cyanophenyl)benzyl]-3-[4-(2'-carboxyphenyl)benzyl]mercapto-5-pentyl-1,2,4-triazole **15**

The title compound was prepared according to the procedure of Example 20, Yield 80%. Mass Spec (DCI) m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S{\cdot}0.5\ H_2O$: C,72.26; H,5.72; N,9.63. found: C,72.25; H,5.69; N,9.56.

EXAMPLE 22

3-[(2'-Cyanophenyl)benzyl]m rcapto]-2-[4-(2'-carboxyphenyl)benzyl]-5-butyl-1,2,4-triazol **29**

The title compound was prepared according to the proc dure of Exampl 20, Yield 89%. Mass Spec (DCl) m/z 559 (M+H). Analysis calc'd for $C_{34}H_{30}N_4O_2S{\cdot}0.5\ H_2O$: C,71.37; H,5.55; N,9.79. found: C,71.28; H,5.64; N,9.61.

EXAMPLE 23

3-[4-(2'-Cyanophenyl)benzyl]mercapto-5-pentyl-1-{4-[2'-(1-triphenylmethyltetrazolophenyl)benzyl]-1,2,4-triazole **43**

3-[4-(2'-Cyanophenyl)benzyl]mercapto-5-pentyl-2-{4-[2'-(1-triphenylmethyltetrazolophenyl)benzyl]-1,2,4-triazole **44**

The title compounds were prepared according to the procedure of Example 8 using 5-pentyl-3-[4-(2'-cyanophenyl)benzyl]mercapto-1,2,4-triazole and 4-[2'-(1-triphenylmethyltetrazolophenyl)benzyl]bromide (Aldrich et al. US Patents No. 4,870,186 and No. 4,874,867).

Compound 43: NMR ($CDCl_3$) shows characteristic benzylic peaks at 5.12 (2H, s) and 4.35 (2H,'s). Compound 44: NMR ($CDCl_3$) shows characteristic benzyl peaks at 5.00 (2H, s) and 4.38 (2H, s).

EXAMPLE 24

3-[4-(2'-Cyanophenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole hemihydrate **36**

3-[4-(2'-Cyanophenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-(-triphenylmethyltetrazolophenyl)benzyl]-1,2,4-triazole (0.6g) was dissolved in THF (15 mL). 3 N HCl (5mL) was added to this solution and the resultant solution was stirred for 16 h at room temperature. The solution was then poured into 50 mL of ether. The ether layer was washed twice with 10% HCl, dried over sodium sulfate, filtered and concentrated to an oil which was chromatographed on silica gel using hexane/ 40% ethyl acetate as the mobile phase. Concentration in vacuo afforded 320 mg (75%) of a white foam found to be the title compound. Mass Spec (DCl) m/z 597 (M+H). Analysis calc'd for :$C_{35}H_{32}N_8S{\cdot}0.5\ H_2O$: C, 69,40; H,5.49; N, 18.50. found: C, 69,43; H, 5.27; N, 18.84.

EXAMPLE 25

3-[4-(2'-Carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-{4-[2'-(1-triphenylmethyltetrazolo)phenyl]benzyl}-1,2,4-triazole **45**

3-[4-(2'-Carbomethoxyphenyl)benzyl]mercapto-5-pentyl-2-{4-[2'-(1-triphenylmethyltetrazolo)phenyl]benzyl}-1,2,4-triazole **46**

The title compounds were prepared according to the procedure of Example 8 using 5-pentyl-3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1,2,4-triazole and 4-[2'-(1-triphenylmethyltetrazolo)phenyl]benzyl}bromide (Aldrich et al. US Patents No. 4,870,186 and No. 4,874,867). Compound 45: NMR ($CDCl_3$) shows characteristic benzylic peaks at 5.14 (2H, s) and 4.34 (2H,'s). Compound 46: NMR ($CDCl_3$) shows characteristic benzylic peaks at 5.00 (2H, s) and 4.40 (2H, s).

EXAMPLE 26

3-[4-(2'-Carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole hemihydrate **16.**

The title compound was prepared according to the procedure of Example 24 using compound 45 in place of compound 43 and was obtained as a white foam, Yield 72%. Mass Spec.(DCl) m/z 630 (M+H). Analysis calc'd for: $C_{35}H_{32}N_8S{\cdot}0.5\ H_2O$ C, 67.69; H,5.68; N,15.35. found: C, 67.72; H,5.69; N, 15.11.

EXAMPLE 27

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzyl]mercapto-5-h xyl-1,2,4-triazol hemihydrate **7**

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzyl]mercapto-5-hexyl-1,2,4-triazole hydrate **24**

The title compounds were prepared according to the procedure of Example 3. Compound 7: Mass Spec (DCI) m/z 634 (M+H). Analysis calc'd for: $C_{38}H_{39}N_3O_4 \cdot H_2O$: C, 71.00; H, 6.27; N,6.53. found: C, 70.96; H,6.47, N,6.81. Compound 24: Mass Spec (DCI) m/z 634 (M+H).

EXAMPLE 28

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylsulfonyl]-5-hexyl-1,2,4-triazole hydrate **37**

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl) benzylmercapto]-5-hexyl-1,2,4-triazole hemihydate (0.2 g, 0.3 mM) was dissolved in methylene chloride and cooled to 0°C. To this solution was added dropwise,a solution of meta-chloroperbenzoic acid (138 mg, 0.8 mM) in 20 mL of methylene chloride. The solution was stirred at 10°C for 2h. 10 mL of 1 N NaOH was added and the layers were separated. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to a solid which was recrystallized from ethyl acetate/ hexane to afford a white-solid, mp 103-105°C

(0.16 g, 76%). Mass Spec. (DCI) m/z 666 (M+H). Analysis: calc'd for $C_{38}H_{39}N_3O_6S \cdot H_2O$: C, 68.56; H, 5.90; N, 6.31. found: C, 68.37; H, 5.87; N, 6.50.

EXAMPLE 29

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-octyl-1,2,4-triazole hydrate **47**

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-octyl-1,2,4-triazole hydrate **48**

The title compounds were prepared according to the procedure of Example 3. Compound 47: Mass Spec: (DCI) m/z 662 (M+H). Compound 48: Mass Spec: (DCI) m/z 662 (M+H).

EXAMPLE 30

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylsulfonyl]-5-octyl-1,2,4-triazole hydrate **49**

The title compound was prepared according to the procedure of Example 28 Mass Spec. (DCI) m/z 694 (M+H). Analysis calc'd for: $C_{40}H_{43}N_3O_6 \cdot H_2O$: C,67.50; H,6.37; N,5.90. found: C,67.72; H,6.05; N, 6.24.

EXAMPLE 31

1-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-octyl-1,2,4-triazole hydrate **38**

The title compound was prepared according to the procedure of Example 11 and was isolated as a white solid, mp 125-128°C. Mass Spec. (DCI) m/z 666 (M+H).

EXAMPLE 32

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylsulfonyl]-5-h ptyl-1,2,4-triazole **50**.

The title compound was prepar d according to the procedure of Exampl 28 and was isolated as a white solid, mp 93-95°C. Mass Sp c (DCI) m/z 680 (M+H). Analysis calc'd for $C_{39}H_{41}N_3O_6S$: C,68.19; H, 5.72; N,6.45.

found: C, 68.55; H, 6.27; N, 6.13.

EXAMPLE 33

1-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-heptyl-1,2,4-triazole hydrate **39**

The title compound was prepared according to the procedure of Example 11 and was isolated as a white solid, mp 158-160°C. Mass Spec. (DCI) m/z 652

EXAMPLE 34

1-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-hexyl-1,2,4-triazole 0.5 hydrate **40**

The title compound was prepared according to the procedure of Example 11 and was isolated as a white solid, mp 118-120°C. Mass Spec. (DCI) m/z 638 (M+H). Analysis calc'd for: $C_{38}H_{35}N_3O_6S{\cdot}0.5\ H_2O$: C, 66.86; H,5.58; N, 6.49; found: C, 66.62; H,5.72; N,6.25.

EXAMPLE 35

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-(2-phenyl)-1,2,4-triazole **41**

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-(2-phenyl)-1,2,4-triazole **42**

The title compounds were prepared according to the procedure of Example 3.Compound 41: Mass Spec (DCI) m/z 652 (M+H). Analysis calc'd for $C_{40}H_{33}N_3O_4S$: C, 73.71; H,5.10; N, 6.45 found: C,73.35; H,5.10; N,6.43. Compound 42: Mass Spec (DCI) m/z 652 (M+H). Analysis calc'd for: $C_{40}H_{33}N_3O_4S$: C, 73.71; H,5.10; N, 6.45. found: 73.46; H,5.45; N,6.21.

EXAMPLE 36

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-(2-phenyl)-1,2,4-triazole hydrate **30**

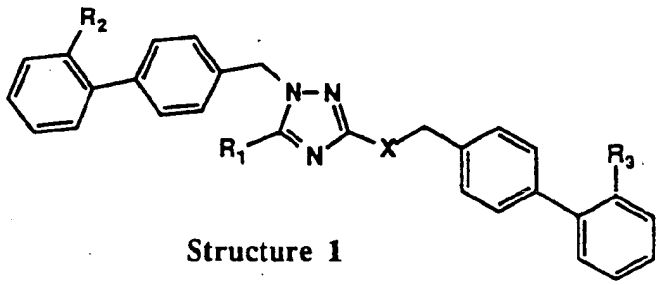
The title compound was prepared according to the procedure of Example 3. Mass Spec (DCI) 626 (M+H). Analysis calc'd for: $C_{38}H_{31}N_3O_4S{\cdot}H_2O$: C, 70.90; H,5.17; N,6.53. found: C,71.37; H,5.06; N,6.59.

EXAMPLE 37

2-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylmercapto]-5-phenyl-1,2,4-triazole hydrate **31**

The title compound was prepared according to the procedure of Example 11. Mass Spec (DCI) m/z 598 (M+H). Analysis calc'd for: $C_{38}H_{27}N_3O_4S{\cdot}H_2O$: C, 70.23; H, 4.75; N, 6.82. found: C, 70.39; H, 4.99; N, 6.50.

Table 1

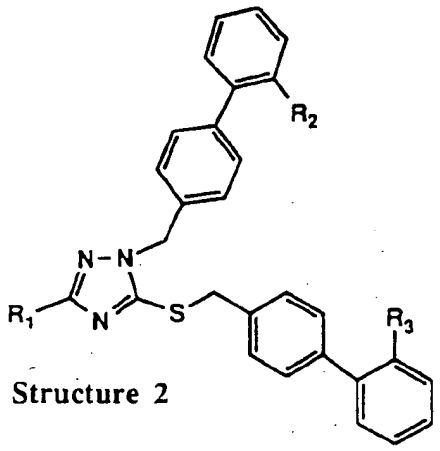


Structure 1

Compound	R_1	R_2	R_3	X
1	n-Bu	CO_2Me	CO_2Me	S
2	n-Bu	CO_2Na	CO_2Na	S
3	i-Bu	CO_2Me	CO_2Me	S
4	i-Bu	CO_2Na	CO_2H	S
5	n-pentyl	CO_2Me	CO_2Me	S
6	n-pentyl	CO_2H	CO_2H	S
7	n-hexyl	CO_2Me	CO_2Me	S
8	n-hexyl	CO_2Me	CO_2Me	S
9	n-heptyl	CO_2Me	CO_2Me	S
10	n-heptyl	CO_2H	CO_2H	S
11	benzyl	CO_2H	CO_2H	S
12	n-pentyl	CO_2H	CN	S
13	n-pentyl	CO_2Me	CN	S
14	n-pentyl	CN	CO_2Me	S
15	n-pentyl	CN	CO_2H	S
16	n-pentyl	tetrazolo	CO_2Me	S
36	n-pentyl	tetrazolo	CN	S
37	n-hexyl	CO_2Me	CO_2Me	SO_2
38	n-octyl	CO_2H	CO_2H	SO_2
39	n-heptyl	CO_2H	CO_2H	SO_2
40	n-hexyl	CO_2H	CO_2H	SO_2
41	2-phenyl ethylene	CO_2Me	CO_2Me	S
43	n-pentyl	1-trityl-tetrazolo	CN	S
45	n-pentyl	1-trityl-	CO_2Me	S

Compound	R_1	R_2	R_3	X
	tetrazolo			
47	n-octyl	CO_2Me	CO_2Me	S
49	n-octyl	CO_2Me	CO_2Me	SO_2

* Monosodium salt position not defined



Structure 2

Compound	R_1	R_2	R_3
17	n-butyl	CO_2Me	CO_2Me
18	n-butyl	CO_2H	CO_2H
19	i-butyl	CO_2Me	CO_2Me
20*	i-butyl	CO_2Na	CO_2H
21	n-pentyl	CO_2Me	CO_2Me
23	n-pentyl	CO_2H	CO_2H
24	n-hexyl	CO_2Me	CO_2Me
25	n-heptyl	CO_2Me	CO_2Me
26*	isobutyl	CO_2Na	CO_2H
27	benzyl	CO_2Me	CO_2Me
28	n-pentyl	CO_2Me	CN
29	n-butyl	CO_2H	CN
30	phenyl	CO_2Me	CO_2Me
31	phenyl	CO_2H	CO_2H
42	2-phenyl ethylene	CO_2Me	CO_2Me

Compound	R_1	R_2	R_3
44	n-pentyl	1-trityl-tetrazolo	CN
46	n-pentyl	1-trityl-tetrazolo	CO_2Me
48	n-octyl	CO_2Me	CO_2Me

*Monosodium salt position not defined

Biological Test Procedures:

Inhibition of Angiotensin II Dose-Response in Rabbit Thoracic Aorta

Purpose: To identify competitive receptor antagonists of an angiotensin II-1 activity, i.e., angiotensin II-induced vasoconstriction in *in vitro* aortic rings.

Procedure: 1.8 to 2.3 kg New Zealand white rabbits are sacrificed with an intravenous sodium pentobarbital overdose and the thoracic aorta gently dissected free from the aortic root to the level of the diaphragm, into ice cold Krebs bicarbonate buffer. The aorta is gently freed of clots and adventitia and cleanly cut with a scalpel into 5 mm segments. Each ring is suspended from a Gould isotonic force transducer in a tissue bath containing 15 mL oxygenated Krebs bicarbonate buffer regulated at 37 °C. Initial tension is adjusted to 4.0 g and equilibrated over three 20-min wash periods to achieve a baseline tension of 3.0 g. Graded angiotensin II doses are given cumulatively to achieve a maximal contraction. Three 20-min washes are performed to remove the initial angiotensin II effect. The test compound is then given at a screening concentration of 1.0×10^{-5} M. After observing any effects of the test compound alone, the angiotensin II cumulative dose-response is then repeated in the presence of the test compound.

Analysis: Angiotensin II vasoconstrictor tension in grams is expressed as a percent of maximal contraction for the before and after test compound angiotensin II dose-responses. Angiotensin II ED50 and ED90 is determined from the angiotensin II dose-response curves generated before and after test compound. A percent inhibition of the angiotensin II dose-response is calculated by determining the percent of maximal contraction occurring after the test compound at the concentration that achieved a 90% contraction before antagonist: 90 - percent contraction occurring after test compound at the ED90 before test compound/90 x 100 = % Inhibition.

Controls: Test compounds are dissolved in DMSO vehicle and DMSO vehicle alone is tested in two rings as a vehicle control in each screening experiment. In this assay, vehicle alone shows a percent inhibition of 5.2 ± 0.7 % (n=23 tests).

Reference Compounds:	
Compound	pA2 (95% C.L.)
DuP-753	8.95 (8.57-9.33)
Saralasin	9.86 (9.21-10.51)

Test Procedure for Screening Potential Angiotensin II Receptor Antagonists in Salt-Depleted Normotensive Rats

Purpose: This test is designed to detect hypotensive effects of a compound after oral dosing in normotensive animals mad r nin-dependent by salt depletion.

Method: Male 350-450 g Sprague-Dawley rats are implanted with teflon microcannulae via th middle caudal artery under 20 mg/kg intravenous brevital anesthesia and permitted a 4-7 day surgical recovery p riod. Throughout recovery and testing animals are individually housed unrestrained in standard rat metabolism cages and receive continuous 0.5 ml/h intra-arterial 0.25 N saline infusion through a spring-shielded swivelling tether connected to an infusion/blood pressure recording system to maintain art rial cannula patency. Animals

are maintained on Low Sodium (0.03%) Purina Rat Chow #5881 throughout the study. After the recovery period animals are given oral 50 mg/kg furosemide (Lasix, Hoechst-Roussel Pharmaceutical) doses on two consecutive days to produc mark d diur sis and plasma volume depl tion that mak s maintenance of normal blood pressure highly d pend nt on function of th renin-angiotensin-aldosterone system. Thr e hours after the second furosemide dos , rats are given test compound uniformly suspended in 1% m thylcellulos (n=3/dos level) or 1 mL 1% methylcellulose vehicle (n=3) orally by gavage and blood pressure is continuously recorded for 24 h using a Buxco computerized data recording system. Compound-induced changes in blood pressure are compared to concurrent vehicle control blood pressures in order to detect drug effect.

Interpretation: Prior to salt depletion, normotensive rats typically show a plasma renin activity (PRA, ng angiotensin I/mL plasma/h, RIA) of 0.7. After the salt-depletion protocol PRA values taken 3 h after the furosemide dose have risen to about 7.4. Whereas blood pressure of normotensive rats that have not been salt-depleted does not change in response to treatment with the nonpeptide angiotensin receptor antagonist, DuP-753, salt-depleted animals typically respond with a blood pressure decrease of about 35 mmHg (mean arterial pressure, MAP). PRA is increased by this DuP-753 treatment to about 41.4.

Compounds that decrease blood pressure 10 or more mmHg (MAP) compared to concurrent control after oral dosing are considered active in this test. Maximum possible response is about -35 mmHg. Compounds that are not orally active are retested by giving a solution dose intra-arterially through the blood pressure cannula three hours after a furosemide dose.

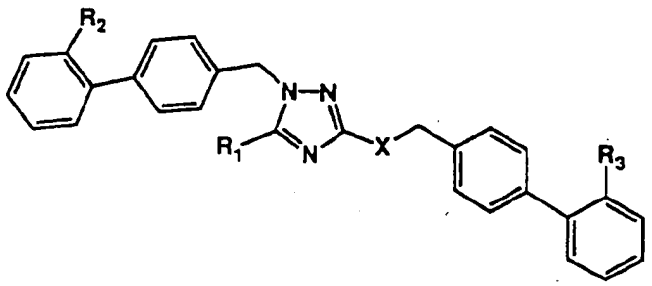
Biological Activity:

Compound	% Inhib. @ 10uM	pA2
2	100	8.49
4	100	7.49
6	100	8.39
8	100	7.96
9	2	-
10	97	6.73
12	79	
21	4	-
23	100	7.19
25	1	-
26	48	5.88
16		5.00
40	100	8.05
38	87	6.09
39	89	6.49

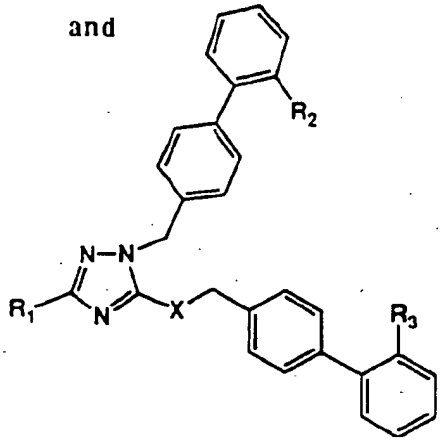
pA2 is the negative logarithm of the antagonist concentration that causes a 2-fold shift to the right (i.e. decrease) in the potency of the agonist or the negative logarithm of the antagonist concentration that cuts the potency of the agonist in half.

Claims

1. A compound of the formula



and



Wherein R_1 is selected from H, C_{1-10} alkyl, C_{2-10} alkenyl, benzyl, phenylalkenyl, substituted benzyl wherein the substituent is selected from C_{1-6} alkyl, NO_2 and halo; phenyl and substituted phenyl wherein the substituent is selected from C_{1-6} alkyl, NO_2, C_{1-6} alkoxy and halo;

R_2 and R_3 are the same or different and are selected from CO_2H, CO_2C_{1-6} alkyl, CN, $CONH_2$, $CON(R_4)_2$ wherein R_4 is C_{1-6} alkyl; 5-tetrazolo, CONHOH and $CONR_4OH$, wherein R_4 is C_{1-6} alkyl; $CONHR_4$ wherein R_4 is 5-tetrazolo and X is selected from S, SO and SO_2.

2. The compound of claim 1 wherein R_1 is C_{1-10} alkyl; R_2 is COOH or 5-tetrazolo and R_3 is COOH, CN or COO_2C_{1-6} alkyl.

3. The compound of claim 1 or claim 2 wherein X is S.

4. The compound of claim 1 or claim 2 wherein X is SO.

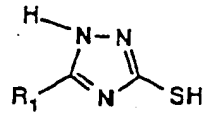
5. The compound of claim 1 or claim 2 wherein X is SO_2.

6. ~~The compound of claim 1 selected from the group consisting of~~ disodium 5-butyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole; 5-pentyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole; 3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole; 3-[4-(2'-cyanophenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole; and 1-[(2'-carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-heptyl-1,2,4-triazole.

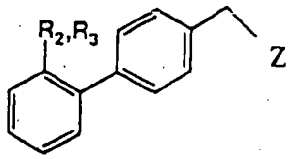
7. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 6 as the active ingredient dispersed in a pharmaceutically acceptable carrier.

8. A compound of any one of claims 1 to 6 for use in treating a physiological condition in a mammal that is mediated by angiotensin II.

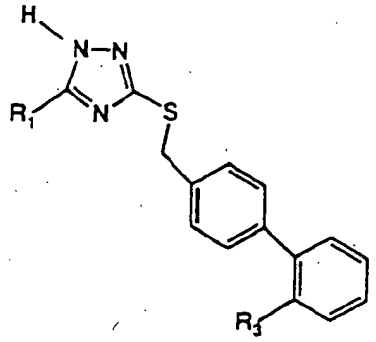
9. A process for preparing a compound of any one of claims 1 to 6,
which comprises reacting a substituted mercaptotriazole of the formula:



with a biphenylyl halide of the formula:

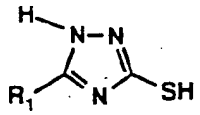


in the presence of one equivalent of a base to form a compound of the formula:

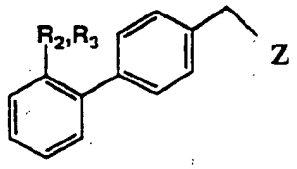


reacting the product formed with a second equivalent of of the base, and the same biphenylyl halide; and optionally oxidising the -S- group to an -SO- or -SO_2- group, wherein Z is selected from bromo and chloro.

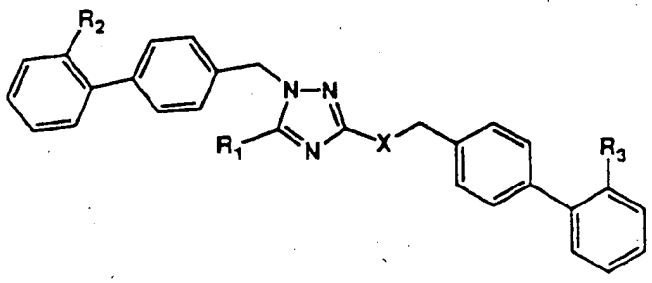
10. A process for preparing a compound of any one of claims 1 to 6.
which comprises reacting one equivalent of a substituted mercaptotriazole of the formula:



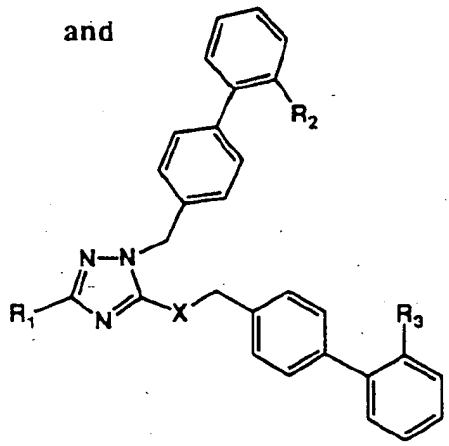
with two equivalents of a biphenylyl halide of the formula:



wherein R_2R_3 is CO_2C_{1-6} alkyl or CN and Z is Cl, Br, or I,
in the pr sence of two equivalents of a base to form a mixture of compounds of the formula:



and



separating the products formed; and optionally oxidising the -S- group to an -SO- or $-SO_2-$ group.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 0661

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,A	WO-A-9 220 662 (MERCK AND CO.) 26 November 1992 * claims *	1,7,8	C07D249/12 C07D403/12 A61K31/41

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

C07D

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	19 APRIL 1993	FRANCOIS J.C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)

(19) Europäisches Patentamt
European Patent Office
Office urop en des br vets

(11) EP 0 554 107 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
11.08.1999 Bulletin 1999/32

(51) Int Cl.[6]: **C07D 249/12**, C07D 403/12, A61K 31/41

(21) Application number: **93300661.1**

(22) Date of filing: **29.01.1993**

(54) Substituted triazoles as angiotensin II inhibitors

Substituierte Triazole als Angiotensin-II-Inhibitoren

Triazoles substitués utiles comme inhibiteurs d'angiotensin II

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU NL SE

(30) Priority: **30.01.1992 US 828394**

(43) Date of publication of application:
04.08.1993 Bulletin 1993/31

(73) Proprietor: **ORTHO PHARMACEUTICAL CORPORATION**
Raritan New Jersey 08869-0602 (US)

(72) Inventors:
- **Bandurco, Victor T.**
  Bridgewater, NJ 08807 (US)
- **Wachter, Michael P.**
  Bloomsbury, NJ 08804 (US)
- **Murray, William V.**
  Belle Mead, NJ 08502 (US)
- **Schwender, Charles F.**
  Califon, NJ 07830 (US)

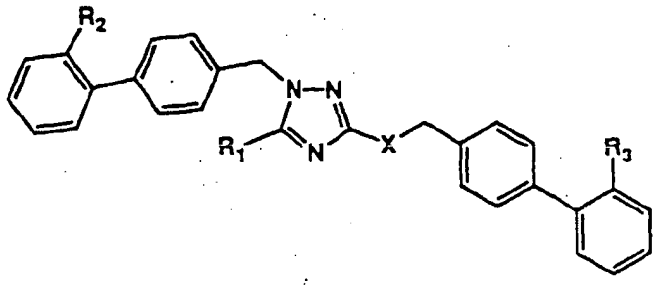
(74) Representative: **Mercer, Christopher Paul et al**
Carpmaels & Ransford
43, Bloomsbury Square
London WC1A 2RA (GB)

(56) References cited:
EP-A- 0 253 310
EP-A- 0 323 841
EP-A- 0 324 377
EP-A- 0 403 158
EP-A- 0 403 159
EP-A- 0 412 594
WO-A-91/00281
WO-A-91/14367
WO-A-92/20662

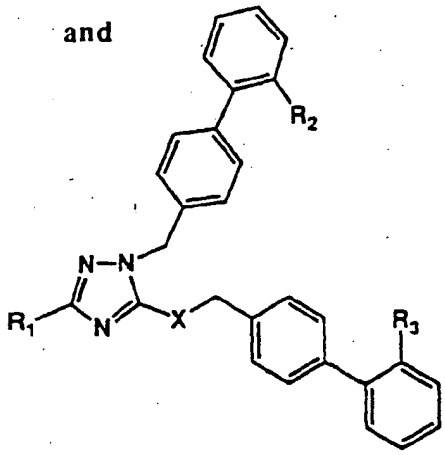
EP 0 554 107 B1

Description

[0001] This invention relates to novel compounds of the following formulae:



and



[0002] The invention also relates to pharmaceutical compositions comprising a compound of the invention as the active ingredient, a method of treating a physiological condition in mammals that is mediated by angiotensin II by administration of a compound of this invention, to novel processes for preparing the compounds of the invention and to pharmaceutically acceptable salts thereof.

[0003] The novel compounds are angiotensin II receptor antagonists and are useful in treating hypertension (lowering of high blood pressure), congestive heart failure, elevated ocular pressure, cerebral stroke, angina, cardiac insufficiency, myocardial infarction and diabetic nephropathy.

[0004] The role of hypertension in cardiac dysfunction is continually evolving. Therefore, the treatment of hypertension continues to be clinically important. The discovery of new agents with fewer undesirable side effects is a therapeutic target since hypertension must be treated chronically. Long term toxicity as well as long term patient compliance are important considerations in the development of new antihypertensive agents.

[0005] One of the blood pressure regulating systems in man is the renin-angiotensin system. The renin-angiotensin system produces angiotensinogen in the kidney which is converted by renin to angiotensin I. The non-vasoconstricting peptide angiotensin I is converted by angiotensin converting enzyme (ACE) to angiotensin II, a potent vasoconstrictor. The discovery of nonpeptide angiotensin converting enzyme (ACE) inhibitors represented an important new step in the treatment of hypertension and several of these inhibitors, such as captopril and enalapril, are widely accepted. Progress toward renin inhibitors as therapeutic agents, however, has been far less successful.

[0006] Direct antagonism of angiotensin II binding at the receptor is an attractive goal because it is the actual vasoconstricting event in this pathway. By inhibiting the receptor, one would expect to have fewer side effects than by inhibiting earlier steps in the pathway. Also, by acting at the receptor, as opposed to one of the enzymes, large deposits of angiotensinogen and angiotensin I should not build up. In some systems, this build up can give rise to shunting mechanisms which can lead to other side effects.

[0007] W092/20662, which forms part of the state of the art by virtue of Article 54(3) EPC, and EP-A-0412594 both describe substituted triazolinone, triazolinethione and triazolineimine compound useful as angiotensin II antagonists.

[0008] EP-A-0323841 describes angiotensin II antagonists, including N-biphenylmethyl substituted triazoles. Preferably, the compounds are 4-biphenylmethyl-1,2,4-triazoles.

[0009] EP-A-0403158 and EP-A-0403159 describe imidazole-5-yl alkenoic acids as angiotensin II antagonists. The imidazol-5-yl ring is optionally substituted with biphenylmethyl at the 1-position of the ring.

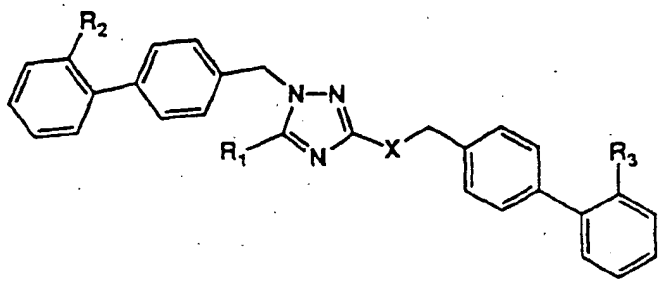
[0010] EP-A-0253310 and EP-A-0324377 describe angiotensin II antagonists that are imidazoles having bulky substituents, especially biphenylmethyl, at the 3-position of the ring. A vast range of possible substituents, including biphenylalkyl, is disclosed for other positions on the imidazole ring. W091/14367 describes the use of these compounds for the further medical application of treating central nervous system disorders.

[0011] W091/00281 describes further imidazole derivatives for use as angiotensin II antagonists. The imidazole ring is preferably substituted with a biphenylmethyl group at the 3-position and a naphthyl group at the 5-position.

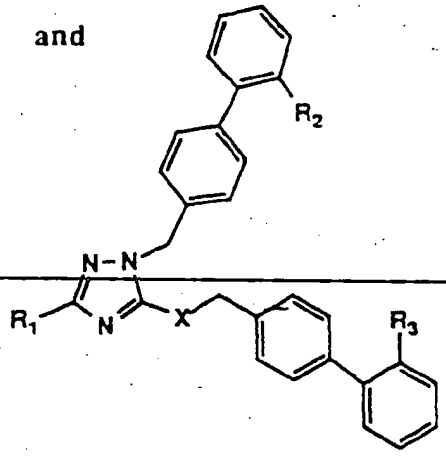
[0012] Duncia et al.[J.Med.Chem., (1990), 33, 1312] Carini et al. [J. Med. Chem. (1990) 33,1330], Johnson et al. [Drug News and Perspectives, (1990), 3, (6),337], Chang et al. (EP-A-0412594) and Robert et al. (GB-A-2234748) all describe compounds which are inhibitors of angiotensin II.

[0013] A number of 3-thio-1,2,4-triazoles have been described in the literature [Beyer, H. et al., Ber. (1960) 637, 135; Kroger, C. et al., Ber (1961) 643, 121 ; and Kroger, C. et al., Ber. (1961) 643, 128; CA99 (21): 175676W; CA 102(25): 216901S; CA 84(5): 29998b; CA83(26): 20942u. None of these compounds, however, is dibenzylated. The compounds of the present invention are bis-biphenyl or phenylphthalamate substituted 3-mercapto-1,2,4-triazoles.

[0014] The present invention provides bis-biphenyl substituted 3-thio-1,2,4-triazoles of the formula:



and



Wherein

R_1 is selected from H, $C_{1\text{-}10}$ alkyl, $C_{2\text{-}10}$ alkenyl, benzyl, substituted benzyl wherein the substituent is selected from $C_{1\text{-}5}$ alkyl, NO_2 and halo such as chloro, bromo, fluoro or iodo; phenyl, phenylalkenyl such as 2-phenylethene or 2-phenylpropylene and substituted phenyl wherein the substituent is selected from $C_{1\text{-}5}$ alkyl, NO_2, $C_{1\text{-}6}$ alkoxy

and halo such as chloro, bromo, fluoro or iodo;

R_2 and R_3 are the same or different and are selected from CO_2H, CO_2C_{1-5} alkyl, CN, $CONH_2$, $CON(R_4)_2$ wherein R_4 is C_{1-6} alkyl; 5-tetrazolo, CONHOH and $CONR_4OH$, wherein R_4 is C_{1-6} alkyl, $CONHR_4$ wherein R_4 is 5-tetrazolo:

and X is selected from S, SO and SO_2.

[0015] The preferred compounds of the invention are those compounds wherein R_1 is C_{1-10} alkyl; R_2 is COOH or 5-tetrazolo and R_3 is CO_2H, CN or CO_2C_{1-6} alkyl.

[0016] The preferred species of the invention are the following compounds:

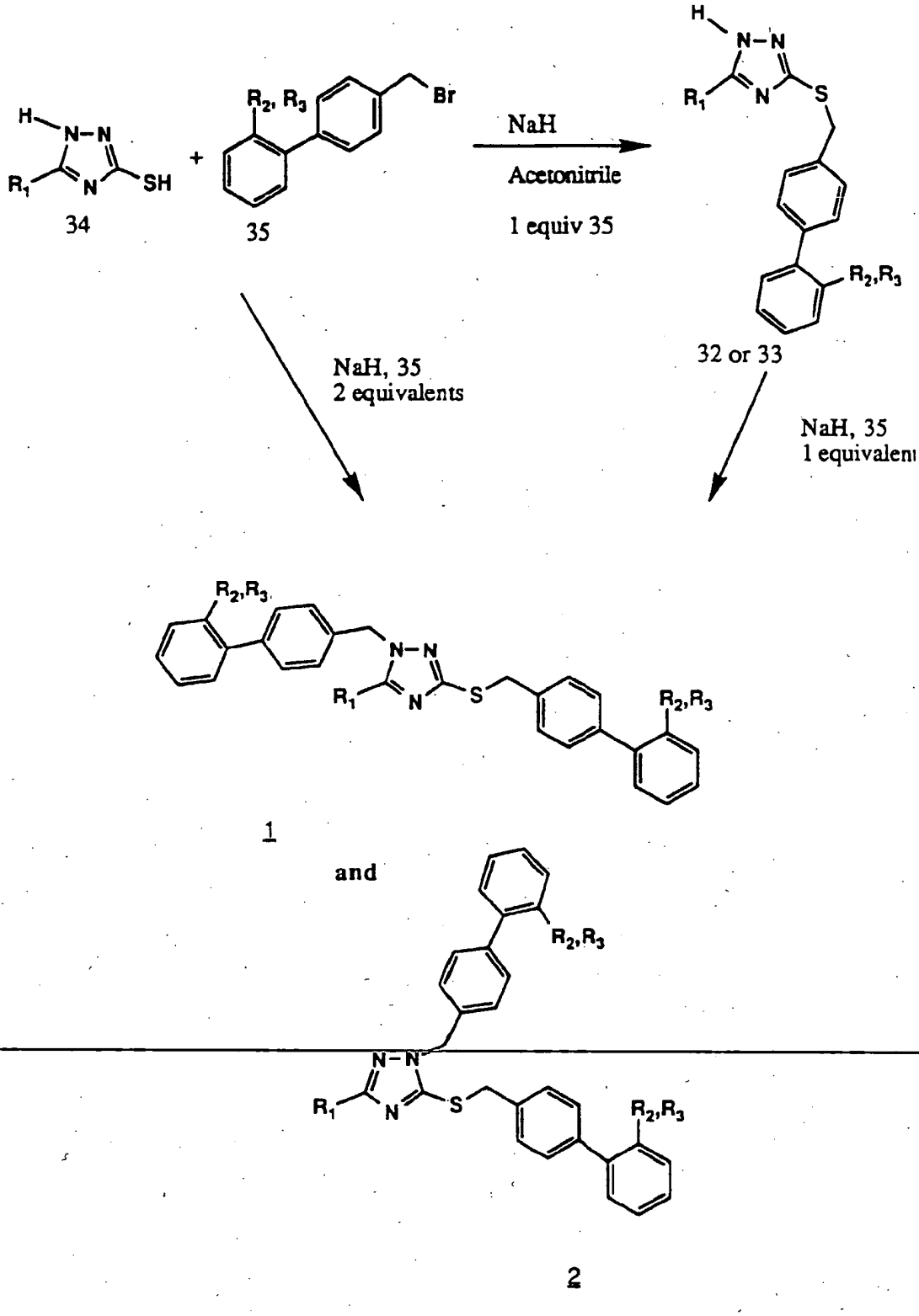
[0017] Disodium 5-butyl-1,3-bis[4-(2'-carboxyphenyi)benzyi]mercapto-1,2,4-triazole; 5-pentyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole; 3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole. 3-[4-(2'-cyanophenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolo-phenyl)benzyl]-1,2,4-triazole; and 1-[(2'-carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-heptyl-1,2,4-triazole.

[0018] The invention also provides novel processes for preparing the novel compounds as disclosed in Scheme1.

[0019] The present invention also provides a pharmaceutical composition comprising an effective amount of a compound according to the invention as the active ingredient, dispersed in a pharmaceutically acceptable carrier.

[0020] The present invention also provides the use of a compound in accordance with the invention for the preparation of a medicament for the treatment of a physiological condition in a mammal that is mediated by angiotensin II.

Scheme 1



[0021] As can be seen from Scheme 1 those compounds wherein X is S are prepared by first reacting a substituted mercaptotriazole with a substituted biphenylylhalide in a suitable solvent such as, for example, acetonitrile, dimethy-

formamide and alcohols such as methanol, in the presence of a base such as, for example, sodium hydride, sodium hydroxide, potassium hydroxide, potassium hydride and potassium carbonate. The reaction mixture is stirred for from about 1-16 hours after which the solvent is removed in vacuo or by other means known to those skilled in the art. The residue is dissolved in an appropriate solvent such as, for example, ether, ethyl acetate or methylene chloride or tetrahydrofuran, and the solution is washed with dilute acid such as, for example, dilute hydrochloric acid, and then washed with water or brine. The solvent is dried and the product is collected by methods known to those skilled in the art; for example, the solution can be crystallized or chromotographed over an adsorbent material such as, for example, silica gel and the product eluted with a suitable solvent. The product obtained is then reacted with a second equivalent of the base and the biphenylylhalide to obtain the substituted triazoles. If in the reaction scheme, two equivalents of the base and the biphenylylhalide are employed, the substituted triazoles are obtained directly and separated and purified by methods known to those skilled in the art.

[0022] Those compounds wherein R_2 or R_3 is $CONH_2$ $CON(R_4)_2$, $CONHR_4$, CONHOH or $CONR_4OH$ are prepared by: (1) converting structure 1 or 2 to an appropriate acid chloride as essentially described by W. Murray et al., in Synthesis (1), 18 (1991) using oxalyl chloride or thionyl chloride in a solvent such as methylene chloride or THF. The acid chloride formed is then added to a solution of the amine such as $HN(C_{1-6}$ alkyl$)_2$, $NH_2(C_{1-6}$ alkyl), benzylamine, 5-aminotetrazole or amine hydrochloride such as $NH_2OH{\cdot}HCl$, $NH(C_{1-6}$ alkyl)OH in an appropriate solvent such as methylene chloride or THF and a base such as triethylamine or pyridine. The amide will generally precipitate out of solution. Hydroxamides wherein R_2 or R_3 is CONHOH or $CONR_4OH$ are isolated by washing with water or dilute acid such as dilute hydrochloric acid, separation of layers, and concentration under reduced pressure.

[0023] The pharmaceutically acceptable salts of the invention include the sodium, potassium and pyridinium salts which are prepared by methods known to those skilled in the art.

[0024] The compounds of the invention where X is SO or SO_2 are prepared by dissolving a compound of structure 1 or 2 in an appropriate solvent such as methylene chloride or tetrachloroethylene. The solution is cooled to between 0 and 10°C and a solvent such as methylene chloride or tetrachloroethylene is added dropwise. To generate the sulfoxide (X=SO) 1 equivalent of metachloroperbenzoic acid in an appropriate solvent (MCPBA) is used. To generate the sulfone (SO_2) two or more equivalents of MCPBA are used. Once the addition is complete the mixture is stirred for between 0 and 6 hours at between 0 and 25°C. Dilute base such as 10% NaOH or 5% KOH is added and the layers are separated. The organic layer is then washed with brine or water, dried over an appropriate drying agent, such as sodium sulfate or magnesium sulfate, filtered and concentrated in vacuo. The residue is then crystallized from an appropriate solvent such as ethyl acetate or ether, or a solvent pair such as ethyl acetate/ hexane or ether/ hexane to afford the pure compound.

[0025] The biphenylylbromides **35** were prepared by the method of Duncia , et al. J. Org. Chem. 1991, 56, 2395-2400 or Aldrich et al US patents 4,870,186 and 4,874,867. The substituted mecaptotriazoles **34** were prepared as described by Von Beyer et al., Leibigs Ann. 637, 135 (1960).

[0026] The compounds of this invention are angiotensin II receptor antagonists, and are useful in treating hypertension (lowering high blood pressure), congestive heart failure, elevated ocular pressure, cerebral stroke, angina, cardiac insufficiency, myocardial infarction and/or diabetic nephropathy.

[0027] Pharmaceutical compositions comprising a compound of the invention as the active ingredient in intimate admixture with a pharmaceutical carrier can be prepared according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., intravenous, oral or parenteral. The composition may also be administered by means of an aerosol. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. For example, in the case of oral liquid preparations (such as suspensions, elixirs and solution), water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. In the case of oral solid preparations (such as, for example, powders, capsules and tablets), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like, may be used. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are preferably employed. If desired, tablets may be sugar-coated or enteric-coated by standard techniques. For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, to aid solubility or for preservative purposes, may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The pharmaceutical compositions will generally be in the form of a dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful and the like, containing from 0.1 to about 1000 mg/kg, and preferably from about 1 to 200 mg/kg of the active ingredient.

[0028] The following experimental examples describe the invention in greater particularity and are intended to be a way of illustrating but not limiting the invention.

In the Examples

[0029] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The infrared spectra (IR) were recorded on a Beckman Instruments IR-B spectrophotometer and are expressed in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra for hydrogen atoms were measured in the indicated solvent with tetramethylsilane (TMS) as the internal standard on a GE QE 300, a Bruker AC 300 or an IBM WP-100 spectrometer. The values are expressed in parts per million downfield from TMS. EI and CI mass spectra were obtained on a Finnigan MAT 8230 Double Focusing high resolution mass spectrometer.

EXAMPLE 1

5-Pentyl-3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **32**

[0030] A mixture of 3-mercapto-5-pentyl-1,2,4-triazole (3.42g, 0.02 mole), sodium hydride 80% in oil (1.0g, 0.033 mole) and 4-(2'-carbomethoxyphenyl)benzylbromide (6.1g, 0.02 mole) was stirred for 6h in acetonitrile (300 mL). The resultant mixture was then filtered through celite, and rotovapped to a brown residue. The residue was chromatographed on silica gel using hexane / 40% ethyl acetate as the mobile phase. Concentration of the eluates afforded 6.5g (82%) of the title compound as a low melting, white, waxy solid. ^{1}HNMR ($CDCl_3$) 7.82 (1H, d, J = 7 Hz); 7.60 - 7.20 (7H, m); 4.38 (2H, s); 3.63 (3H, s); 2.78 (2H, t, J = 7 Hz); 1.70 (2H, m); 1.4 (4H, m); 1.31 (3H, t, J = 4 Hz). Mass Spec (DCI) m/z 396 (M+H). Analysis calc'd for $C_{22}H_{25}N_3O_2S$: C,66.82; H,6.32; N,10.00. found: C,66.67; H,6.34; N, 10.00.

EXAMPLE 2

5-Pentyl-3-[4-(2'-cyanophenyl)benzyl]mercapto-1,2,4-triazole **33**

[0031] The title compound was prepared following the procedure of Example 1 using 4-(2-cyanophenyl)benzylbromide as the biphenylylbromide, Yield 88%, mp 105-106°C. Mass Spec (DCI) m/z 363 (M+H). Analysis calc'd for $C_{21}H_{22}N_4S$: C,69.56; H,6.12; N,15.46. found: C,69.59; H,5.91; N,15.34.

EXAMPLE 3

5-Pentyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **21** and 5-Pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **5**.

[0032]

A) A mixture of 5-pentyl-3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole (3.95g, 0.01 mole), sodium hydride 80% (0.5g, 0.01 mole) and 4-(2-carbomethoxyphenyl)benzylbromide (3.04g, 0.01 mole) were combined in 350 mL of acetonitrile.and the mixture was refluxed for 5h. The resulting mixture was filtered through celite and rotovapped to a brown residue. The residue was chromatographed on silica gel using hexane / 30% ethyl acetate as the mobile phase. Concentration of the eluates afforded 5-pentyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl] mercapto-1,2,4-triazole **21** as a colorless oil (1.36g, 22%) and 5-pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl] mercapto-1,2,4-triazole **5** as a colorless oil (2.52g, 41%).

B) A mixture of 3-mercapto-5-pentyl-1,2,4-triazole (1.71g, 0.01 mole), sodium hydride, 80% in oil (1.0g, 0.033 mole) and 4-(2'-carbomethoxyphenyl)benzylbromide (6.1g, 0.02 mole) was refluxed for 8h in acetonitrile (300 mL). The resultant mixture was then filtered through celite,and rotovapped to a brown residue. The residue was chromatographed on silica gel using hexane / 30% ethyl acetate as the mobile phase. Concentration of the eluates afforded 5-pentyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **21** (0.9g, 15%) and 5-pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **5** (1.02g, 16%) as colorless oils.

[0033] Compound 21: ^{1}NMR ($CDCl_3$) 7.82 (2H, m); 7.6 - 7.2 (14H, m); 5.16 (2H, s); 4.51 (2H, s); 3.63 (3H, s); 3.60 (3H, s); 2.76 (2H, t, J = 7 Hz); 1.78 (2H, m); 1.40 (4H, m); 1.31 (3H, m). Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{37}N_3O_4S \cdot 1/2\ H_2O$: C,70.68; H,6.09; N,6.68. found: C,70.47; H,5.59; N,6.90.

[0034] Compound 5: ^{1}HNMR ($CDCl_3$) 7.82 (2H, m); 7.6-7.15 (14H, m); 5.24 (2H, s); 4.41 (2H, s); 3.62 (3H, s); 3.60 (3H, s); 2.67 (2H, t, J = 7 Hz); 1.65 (2H, m); 1.35 (4H, m); 0.85 (3H, t, J = 4 Hz). NOE enhancement of 2.67 t when 5.24 s irradiated. Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{37}N_3O_4S \cdot H_2O$: C,69.69; H,6.16; N,6.59.

found: C,69.32; H,6.00; N,6.86.

EXAMPLE 4

5-Butyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **17**

5-Butyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **1**

[0035] The title compounds were prepared by following the procedure of Example 3.

[0036] Compound 17: Mass Spec (DCI) m/z 606 (M+H). Analysis calc'd for $C_{36}H_{35}N_3O_4S \cdot 1/2\ H_2O$: C,70.34; H,5.90; N,6.83. found: C, 70.60; H,6.06; N,7.12.

[0037] Compound 1: Mass Spec (DCI) m/z 606 (M+H). Analysis calc'd for $C_{36}H_{35}N_3O_4S$: C,71.39; H,5.82; N,6.94. found: C,70.90; H, 5.22; n,7.16.

EXAMPLE 5

5-Isobutyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **19**

5-Isobutyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **3**

[0038] The title compounds were prepared by following the procedure (B) of Example 3.

[0039] Compound 19: Mass Spec (DCI) m/z 606 (M+H)

[0040] Compound 3: Mass Spec (DCI) m/z 606 (M+H). Analysis calc'd for $C_{36}H_{35}N_3O_4S \cdot 1/2\ H_2O$: C,70.34; H,5.90; N,6.83. found: C,70.30; H,5.66; N,7.12.

EXAMPLE 6

5-Hexyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **24**

5-Hexyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **8**

[0041] The title compounds were prepared by following the procedure (B) of Example 3.

[0042] Compound 24: Mass Spec (DCI) m/z 634 (M+H)

[0043] Compound 8: Mass Spec (DCI) m/z 634 (M+H). Analysis calc'd for $C_{39}H_{39}N_3O_4S \cdot 1/2\ H_2O$: C,71.00; H,6.27; N,6.53. found: C,70.96; H,6.47; N,6.81.

EXAMPLE 7

5-Heptyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **25**

5-Heptyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **9**

[0044] The title compounds were prepared by following the procedure (B) of Example 3.

[0045] Compound 9: Mass Spec (DCI) m/z 648 (M+H). Analysis calc'd for $C_{39}H_{41}N_3O_4S \cdot 1/2\ H_2O$: C,71.32; H,6.44; N,6.40. found: C,71.31; H,6.38; 6.96.

[0046] Compound 25: Mass Spec (DCI) m/z 648 (M+H). Analysis calc'd for $C_{39}H_{41}\ N_3O_4S \cdot 1/2\ H_2O$: C,71.32; H,6.44; N,6.40. found: C,71.25; H, 6.73; N,6.63.

EXAMPLE 8

3-[(2'-Cyanophenyl)benzyl]mercapto]-2-(2'-carbomethoxyphenyl)benzyl-5-butyl-1,2,4-triazole **28**

3-[(2'-Cyanophenyl)benzyl]mercapto]-1-(2'-carbomethoxyphenyl)benzyl-5-butyl-1,2,4-triazole **13**

[0047] The title compounds were prepared by following procedure (A) of Example 3 using compound 33 in place of compound 32.

[0048] Compound 28: Mass Spec (DCI) m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S \cdot 0.25\ H_2O$: C,72.81; H, 5.68; N,9.70. found: C,72.66; H,5.79; N,9.92.

[0049] Compound 13: Mass Spec (DCI) m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S \cdot 0.25\ H_2O$: C,72.81; H, 5.68; N,9.70. found: C,72.81; H,5.78; N,10.15.

EXAMPLE 9

5-Benzyl-2,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole **27**

[0050] The title compound was prepared by following the procedure (B) of Example 3.
[0051] Compound 27: Mass Spec (DCI) m/z 640 (M+H). Analysis calc'd for: C,73.22; H,5.20; N,6.57. found: C,73.16; H,5,25; N,6.10.

EXAMPLE 10

3-[(2'-Cyanophenyl)benzyl]mercapto]-1-(2'-carbomethoxyphenyl)benzyl-5-pentyl-1,2,4-triazole **14**

[0052] The title compound was prepared by following the procedure of Example 8.
[0053] Compound 14: Mass Spec (DCI) m/z 587 (M+H). Analysis calc'd for $C_{36}H_{34}N_4O_2S$: C,73.69; H,5.84; N,9.55. found: C,73.54; H,5.94; N,9.46.

EXAMPLE 11

5-Pentyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **6**

[0054] 5-Pentyl-1,3-bis-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-1,2,4-triazole (1.24g, 0.002 mole) was dissolved in methanol (35mL), 30% KOH (10ml) was added to this solution and the reaction was refluxed for 8h. The resultant mixture was concentrated in vacuo and partitioned between methylene chloride and water (50 mL each). The methylene chloride layer was removed and the aqueous layer was acidified to pH 1 with dilute HCl. The aqueous layer was extracted with 3 portions of methylene chloride (50 mL each), dried over sodium sulfate, filtering and concentrated to a yellow foam (1.0g, (83%). Mass Spec (DCI) m/z 592 (M+H). Analysis calc'd for $C_{35}H_{32}N_3O_4S \cdot 2H_2O$: C,66.97; H, 5.63; N,6.69. found: C,67.06; H,5.76; N,6.39.

EXAMPLE 12

5-Pentyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **23**

[0055] The title compound was prepared according to the procedure of Example 11. Yield 72 %, mp 116-120 °C. Mass Spec (DCI) m/z 592 (M+H). Analysis calc'd for $C_{35}H_{32}N_3O_4S \cdot H_2O$: C,68.95; H,5.79; N,6.89. found: C,68.80; H, 5.41; N,7.12.

EXAMPLE 13

5-Butyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **18**

[0056] The title compound was prepared according to the procedure of Example 11. mp 118 - 122 °C. Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{31}N_3O_4S$: C,70.70; H,5.41; N,7.27. found: C,70.17; H,5.00; N,7.29.

EXAMPLE 14

Disodium 5-Butyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **2**

[0057] The title compound was prepared according to the procedure of Example 11. The sodium salt was formed by dissolving the triazole in methanol containing 2 equivalents of sodium methoxide and subsequent concentration in vacuo. mp 235°C. Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{29}N_3O_4SNa_2 \cdot 1.25\ H_2O$: C,63.39; H,4.93; N6.50; found: C,63.11; H,4.90; N,6.89.

EXAMPLE 15

Sodium 5-isobutyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **4**

[0058] The title compound was prepared according to the procedure of Example 11. The sodium salt was formed by dissolving the triazole in methanol containing 1 equivalent of sodium methoxide and subsequent concentration in vacuo. mp 143 °C (dec.). Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{30}N_3O_4SNa \cdot 2\ H_2O$: C,64.23; H,5.23: N, 6.60; found: C,64.66; H,4.99; N,6.69.

EXAMPLE 16

Sodium 5-isobutyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **20**

[0059] The title compound was prepared according to the procedure of Example 11. The sodium salt was formed by dissolving the triazole in methanol containing 1 equivalent of sodium methoxide and subsequent concentration in vacuo. mp 140°C (dec.). Mass Spec (DCI) m/z 578 (M+H). Analysis calc'd for $C_{34}H_{30}N_3O_4SNa \cdot H_2O$: C,66.10; H,5.38; N,6.80. found: C,65.81; H,5.10; N,6.84.

EXAMPLE 17

5-Heptyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **10**

[0060] The title compound was prepared according to the procedure of Example 11. mp 78 - 80°C. Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{37}N_3O_4S \cdot 2\ H_2O$: C,67.77; H,6.30; N,6.41. found: C,68.09; H,6.17; N,5.98.

EXAMPLE 18

Sodium 5-isobutyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **26**

[0061] The title compound was prepared following the procedure of Example 11. The sodium salt was formed by dissolution in methanol containing 1 equivalent of sodium methoxide and subsequent concentration in vacuo. mp 110 °C (dec.). Mass Spec (DCI) m/z 620 (M+H). Analysis calc'd for $C_{37}H_{36}N_3O_4SNa \cdot 1.5H_2O$: C,66.45; h,6.02; N,6.28. found: C,66.27; H,5.59; N,6.12.

EXAMPLE 19

5-Benzyl-2,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole **11**

[0062] The title compound was prepared according to the procedure of Example 11. Mass Spec (DCI) m/z 612 (M+H). Analysis calc'd for $C_{37}H_{29}N_3O_4S \cdot 0.4\ H_2O$: C,71.80; H,4,85; N,6.79. found: C,72.02; H,5.14; N,6.39.

EXAMPLE 20

3-[4-(2'-Cyanophenyl)benzyl]mercapto]-1-[4-(2'-carboxyphenyl)benzyl]-5-pentyl-1,2,4-triazole **12**

[0063] 5-Pentyl-1,3-bis-[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole (1.18g, 0.002 mole) was dissolved in methanol (35mL). 30% KOH (10mL) was added to this solution and the reaction mixture was refluxed for 2h. The resultant mixture was concentrated in vacuo and partitioned between methylene chloride and water (50 mL each). The methylene chloride layer was removed and the aqueous layer was acidified to pH 1 with dilute HCl. The aqueous layer was extracted with 3 portions of methylene chloride (50 mL each), dried over sodium sulfate, filtered and concentrated to a white foam (1.0g, 88% yield). Mass Spec (DCI) m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S \cdot 0.25\ H_2O$: C, 72.83; H,5.68; N,9.71. found: C,72.58; H,5.66; N,9.68.

EXAMPLE 21

1-[(2'-Cyanophenyl)benzyl]-3-[4-(2'-carboxyphenyl)benzyl]mercapto-5-pentyl-1,2,4-triazole **15**

[0064] The title compound was prepared according to the procedure of Example 20, Yield 80%. Mass Spec (DCI)

m/z 573 (M+H). Analysis calc'd for $C_{35}H_{32}N_4O_2S{\cdot}0.5\ H_2O$: C,72.26; H,5.72; N,9.63. found: C,72.25; H,5.69; N,9.56.

EXAMPLE 22

3-[(2'-Cyanophenyl)benzyl]mercapto]-2-[4-(2'-carboxyphenyl)benzyl]-5-butyl-1,2,4-triazole **29**

[0065] The title compound was prepared according to the procedure of Example 20, Yield 89%. Mass Spec (DCI) m/z 559 (M+H). Analysis calc'd for $C_{34}H_{30}N_4O_2S{\cdot}0.5\ H_2O$: C,71.37; H,5.55; N,9.79. found: C,71.28; H,5.64; N,9.61.

EXAMPLE 23

3-[4-(2'-Cyanophenyl)benzyl]mercapto-5-pentyl-1-{4-[2'-(1-triphenylmethyltetrazolophenyl)benzyl]-1,2,4-triazole **43**

3-[4-(2'-Cyanophenyl)benzyl]mercapto-5-pentyl-2-{4-[2'-(1-triphenylmethyltetrazolophenyl)benzyl]-1,2,4-triazole **44**

[0066] The title compounds were prepared according to the procedure of Example 8 using 5-pentyl-3-[4-(2'-cyanophenyl)benzyl]mercapto-1,2,4-triazole and 4-[2'-(1-triphenylmethyltetrazolophenyl)benzyl]bromide (Aldrich et al. US Patents No. 4,870,186 and No. 4,874,867).

[0067] Compound 43: NMR ($CDCl_3$) shows characteristic benzylic peaks at 5.12 (2H, s) and 4.35 (2H,'s). Compound 44: NMR ($CDCl_3$) shows characteristic benzyl peaks at 5.00 (2H, s) and 4.38 (2H, s).

EXAMPLE 24

3-[4- (2'-Cyanophenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole hemihydrate **36**

[0068] 3-[4-(2'-Cyanophenyl)benzyl)mercapto-5-pentyl-1-[4-(2'-(-triphenylmethyltetrazolophenyl)benzyl]-1,2,4-triazole (0.6 g) was dissolved in THF (15 mL). 3 N HCl (5mL) was added to this solution and the resultant solution was stirred for 16 h at room temperature. The solution was then poured into 50 mL of ether. The ether layer was washed twice with 10% HCl, dried over sodium sulfate, filtered and concentrated to an oil which was chromatographed on silica gel using hexane/ 40% ethyl acetate as the mobile phase. Concentration in vacuo afforded 320 mg (75%) of a white foam found to be the title compound. Mass Spec (DCI) m/z 597 (M+H). Analysis calc'd for :$C_{35}H_{32}N_8S{\cdot}0.5\ H_2O$: C, 69.40; H,5.49; N, 18.50. found: C, 69.43; H, 5.27; N, 18.84.

EXAMPLE 25

3-[4-(2'-Carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-{4-[2'-(1-triphenylmethyltetrazolo)phenyl]benzyl}-1,2,4-triazole **45**

3-[4- (2'-Carbomethoxyphenyl)benzyl]mercapto-5-pentyl-2-{4-[2'-(1-triphenylmethyltetrazolo)phenyl]benzyl}-1,2,4-triazole **46**

[0069] The title compounds were prepared according to the procedure of Example 8 using 5-pentyl-3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1,2,4-triazole and 4-[2'-(1-triphenylmethyltetrazolo)phenyl]benzyl}bromide (Aldrich et al. US Patents No. 4,870,186 and No. 4,874,867). Compound 45: NMR ($CDCl_3$) shows characteristic benzylic peaks at 5.14 (2H, s) and 4.34 (2H,'s). Compound 46: NMR ($CDCl_3$) shows characteristic benzylic peaks at 5.00 (2H, s) and 4.40 (2H, s).

EXAMPLE 26

3-[4-(2'-Carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1 -[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole hemihydrate **16.**

[0070] The title compound was prepared according to the procedure of Example 24 using compound 45 in place of compound 43 and was obtained as a white foam, Yield 72%. Mass Spec.(DCI) m/z 630 (M+H). Analysis calc'd for: $C_{35}H_{32}N_8S{\cdot}0.5\ H_2O$ C, 67.69; H,5.68; N,15.35. found: C, 67.72; H,5.69; N, 15.11.

EXAMPLE 27

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzyl]mercapto-5-hexyl-1,2,4-triazole hemihydrate **7**

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzyl]mercapto-5-hexyl-1,2,4-triazole hydrate **24**

[0071] The title compounds were prepared according to the procedure of Example 3. Compound 7: Mass Spec (DCI) m/z 634 (M+H). Analysis calc'd for: $C_{38}H_{39}N_3O_4 \cdot H_2O$: C, 71.00; H, 6.27; N,6.53. found: C, 70.96; H,6.47, N,6.81. Compound 24: Mass Spec (DCI) m/z 634 (M+H).

EXAMPLE 28

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylsulfonyl]-5-hexyl-1,2,4-triazole hydrate **37**

[0072] 1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl) benzylmercapto]-5-hexyl-1,2,4-triazole hemihydate (0.2 g, 0.3 mM) was dissolved in methylene chloride and cooled to 0°C. To this solution was added dropwise,a solution of meta-chloroperbenzoic acid (138 mg, 0.8 mM) in 20 mL of methylene chloride. The solution was stirred at 10°C for 2h . 10 mL of 1 N NaOH was added and the layers were separated. The organic layer was washed with brine, dried over sodium sulfate, filtered and concentrated to a solid which was recrystallized from ethyl acetate/hexane to afford a white-solid, mp 103-105°C

[0073] (0.16 g, 76%). Mass Spec. (DCI) m/z 666 (M+H). Analysis: calc'd for $C_{38}H_{39}N_3O_6S \cdot H_2O$: C, 68.56; H, 5.90; N, 6.31. found: C, 68.37; H, 5.87; N, 6.50.

EXAMPLE 29

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-octyl-1,2,4-triazole hydrate **47**

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-octyl-1,2,4-triazole hydrate **48**

[0074] The title compounds were prepared according to the procedure of Example 3. Compound 47: Mass Spec: (DCI) m/z 662 (M+H). Compound 48: Mass Spec: (DCI) m/z 662 (M+H).

EXAMPLE 30

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylsulfonyl]-5-octyl-1,2,4-triazole hydrate **49**

[0075] The title compound was prepared according to the procedure of Example 28 Mass Spec. (DCI) m/z 694 (M+H). Analysis calc'd for: $C_{40}H_{43}N_3O_6 \cdot H_2O$: C,67.50; H,6.37; N,5.90. found: C,67.72; H,6.05; N, 6.24.

EXAMPLE 31

1-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-octyl-1,2,4-triazole hydrate **38**

~~**[0076]** The title compound was prepared according to the procedure of Example 11 and was isolated as a white~~ solid, mp 125-128°C. Mass Spec. (DCI) m/z 666 (M+H).

EXAMPLE 32

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylsulfonyl]-5-heptyl-1,2,4-triazole **50**.

[0077] The title compound was prepared according to the procedure of Example 28 and was isolated as a white solid, mp 93-95°C. Mass Spec (DCI) m/z 680 (M+H). Analysis calc'd for $C_{39}H_{41}N_3O_6S$: C,68.19; H, 5.72; N,6.45. found: C, 68.55; H, 6.27; N, 6.13.

EXAMPLE 33

1-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-heptyl-1,2,4-triazole hydrate **39**

[0078] The title compound was prepared according to the procedure of Example 11 and was isolated as a white solid, mp 158-160°C. Mass Spec. (DCI) m/z 652

EXAMPLE 34

1-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-hexyl-1,2,4-triazole 0.5 hydrate **40**

[0079] The title compound was prepared according to the procedure of Example 11 and was isolated as a white solid, mp 118-120°C. Mass Spec. (DCI) m/z 638 (M+H). Analysis calc'd for: $C_{36}H_{35}N_3O_6S \cdot 0.5\ H_2O$: C, 66.86; H,5.58; N, 6.49; found: C, 66.62; H,5.72; N,6.25.

EXAMPLE 35

1-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-(2-phenyl)-1,2,4-triazole **41**

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-(2-phenyl)-1,2,4-triazole **42**

[0080] The title compounds were prepared according to the procedure of Example 3.Compound 41: Mass Spec (DCI) m/z 652 (M+H). Analysis calc'd for $C_{40}H_{33}N_3O_4S$: C, 73.71; H,5.10; N, 6.45 found: C,73.35; H,5.10; N,6.43. Compound 42: Mass Spec (DCI) m/z 652 (M+H). Analysis calc'd for: $C_{40}H_{33}N_3O_4S$: C, 73.71; H,5.10; N, 6.45. found: 73.46; H,5.45; N,6.21.

EXAMPLE 36

2-[(2'-Carbomethoxyphenyl)benzyl]-3-[(2'-carbomethoxyphenyl)benzylmercapto]-5-(2-phenyl)-1,2,4-triazole hydrate **30**

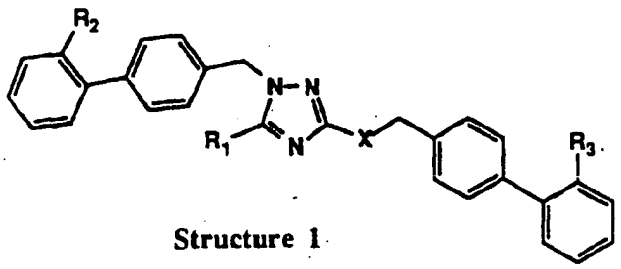
[0081] The title compound was prepared according to the procedure of Example 3. Mass Spec (DCI) 626 (M+H). Analysis calc'd for: $C_{38}H_{31}N_3O_4S \cdot H_2O$: C, 70.90; H,5.17; N,6.53. found: C,71.37; H,5.06; N,6.59.

EXAMPLE 37

2-[(2'-Carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylmercapto]-5-phenyl-1,2,4-triazole hydrate **31**

[0082] The title compound was prepared according to the procedure of Example 11. Mass Spec (DCI) m/z 598 (M+H). Analysis calc'd for: $C_{36}H_{27}N_3O_4S \cdot H_2O$: C, 70.23; H, 4.75; N, 6.82. found: C, 70.39; H, 4.99; N, 6.50.

Table 1

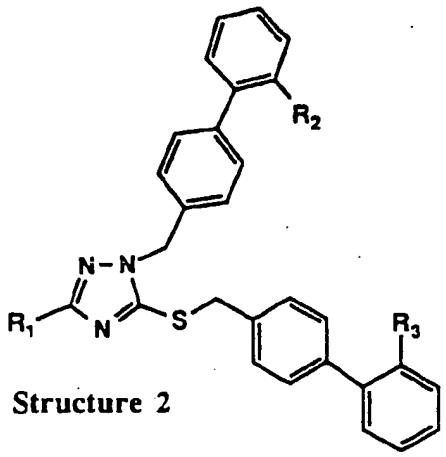


Structure 1

Compound	R_1	R_2	R_3	X
1	n-Bu	CO_2Me	CO_2Me	S
2	n-Bu	CO_2Na	CO_2Na	S
3	i-Bu	CO_2Me	CO_2Me	S
4*	i-Bu	CO_2Na	CO_2H	S
5	n-pentyl	CO_2Me	CO_2Me	S
6	n-pentyl	CO_2H	CO_2H	S
7	n-hexyl	CO_2Me	CO_2Me	S
8	n-hexyl	CO_2Me	CO_2Me	S
9	n-heptyl	CO_2Me	CO_2Me	S
10	n-heptyl	CO_2H	CO_2H	S
11	benzyl	CO_2H	CO_2H	S
12	n-pentyl	CO_2H	CN	S
13	n-pentyl	CO_2Me	CN	S
14	n-pentyl	CN	CO_2Me	S
15	n-pentyl	CN	CO_2H	S
16	n-pentyl	tetrazolo	CO_2Me	S
36	n-pentyl	tetrazolo	CN	S
37	n-hexyl	CO_2Me	CO_2Me	SO_2
38	n-octyl	CO_2H	CO_2H	SO_2
39	n-heptyl	CO_2H	CO_2H	SO_2
40	n-hexyl	CO_2H	CO_2H	SO_2
41	2-phenyl ethylene	CO_2Me	CO_2Me	S
43	n-pentyl	1-trityl-tetrazolo	CN	S
45	n-pentyl	1-trityl-	CO_2Me	S

Compound	R_1	R_2	R_3	X
	tetrazolo			
47	n-octyl	CO_2Me	CO_2Me	S
49	n-octyl	CO_2Me	CO_2Me	SO_2

* Monosodium salt position not defined



Structure 2

Compound	R_1	R_2	R_3
17	n-butyl	CO_2Me	CO_2Me
18	n-butyl	CO_2H	CO_2H
19	i-butyl	CO_2Me	CO_2Me
20*	i-butyl	CO_2Na	CO_2H
21	n-pentyl	CO_2Me	CO_2Me
23	n-pentyl	CO_2H	CO_2H
24	n-hexyl	CO_2Me	CO_2Me
25	n-heptyl	CO_2Me	CO_2Me
26*	isobutyl	CO_2Na	CO_2H
27	benzyl	CO_2Me	CO_2Me
28	n-pentyl	CO_2Me	CN
29	n-butyl	CO_2H	CN
30	phenyl	CO_2Me	CO_2Me
31	phenyl	CO_2H	CO_2H
42	2-phenyl ethylene	CO_2Me	CO_2Me

Compound	R_1	R_2	R_3
44	n-pentyl	1-trityl-tetrazolo	CN
46	n-pentyl	1-trityl-tetrazolo	CO_2Me
48	n-octyl	CO_2Me	CO_2Me

*Monosodium salt position not defined

Biological Test Procedures:

Inhibition of Angiotensin II Dose-Response in Rabbit Thoracic Aorta

[0083] Purpose: To identify competitive receptor antagonists of an angiotensin II-1 activity, i.e., angiotensin II-induced vasoconstriction in *in vitro* aortic rings.

[0084] Procedure: 1.8 to 2.3 kg New Zealand white rabbits are sacrificed with an intravenous sodium pentobarbital overdose and the thoracic aorta gently dissected free from the aortic root to the level of the diaphragm, into ice cold Krebs bicarbonate buffer. The aorta is gently freed of clots and adventitia and cleanly cut with a scalpel into 5 mm segments. Each ring is suspended from a Gould isotonic force transducer in a tissue bath containing 15 mL oxygenated Krebs bicarbonate buffer regulated at 37 °C. Initial tension is adjusted to 4.0 g and equilibrated over three 20-min wash periods to achieve a baseline tension of 3.0 g. Graded angiotensin II doses are given cumulatively to achieve a maximal contraction. Three 20-min washes are performed to remove the initial angiotensin II effect. The test compound is then given at a screening concentration of 1.0×10^{-5} M. After observing any effects of the test compound alone, the angiotensin II cumulative dose-response is then repeated in the presence of the test compound.

[0085] Analysis: Angiotensin II vasoconstrictor tension in grams is expressed as a percent of maximal contraction for the before and after test compound angiotensin II dose-responses. Angiotensin II ED50 and ED90 is determined from the angiotensin II dose-response curves generated before and after test compound. A percent inhibition of the angiotensin II dose-response is calculated by determining the percent of maximal contraction occurring after the test compound at the concentration that achieved a 90% contraction before antagonist: 90 - percent contraction occurring after test compound at the ED90 before test compound/90 x 100 = % Inhibition.

[0086] Controls: Test compounds are dissolved in DMSO vehicle and DMSO vehicle alone is tested in two rings as a vehicle control in each screening experiment. In this assay, vehicle alone shows a percent inhibition of 5.2 ± 0.7 % (n=23 tests).

Reference Compounds:	
Compound	pA2 (95% C.L.)
DuP-753	8.95 (8.57-9.33)
Saralasin	9.86 (9.21-10.51)

Test Procedure for Screening Potential Angiotensin II Receptor Antagonists in Salt-Depleted Normotensive Rats

[0087] Purpose: This test is designed to detect hypotensive effects of a compound after oral dosing in normotensive animals made renin-dependent by salt depletion.

[0088] Method: Male 350-450 g Sprague-Dawley rats are implanted with teflon microcannulae via the middle caudal artery under 20 mg/kg intravenous brevital anesthesia and permitted a 4-7 day surgical recovery period. Throughout recovery and testing animals are individually housed unrestrained in standard rat metabolism cages and receive continuous 0.5 ml/h intra-arterial 0.25 N saline infusion through a spring-shielded swivelling tether connected to an infusion/blood pressure recording system to maintain arterial cannula patency. Animals are maintained on Low Sodium (0.03%) Purina Rat Chow #5881 throughout the study. After the recovery period animals are given oral 50 mg/kg furosemide (Lasix, Hoechst-Roussel Pharmaceutical) doses on two consecutive days to produce marked diuresis and plasma

volume depletion that makes maintenance of normal blood pressure highly dependent on function of the renin-angiotensin-aldosterone system. Three hours after the second furosemide dose, rats are given test compound uniformly suspended in 1% methylcellulose (n=3/dose level) or 1 mL 1% methylcellulose vehicle (n=3) orally by gavage and blood pressure is continuously recorded for 24 h using a Buxco computerized data recording system. Compound-induced changes in blood pressure are compared to concurrent vehicle control blood pressures in order to detect drug effect.

[0089] Interpretation: Prior to salt depletion, normotensive rats typically show a plasma renin activity (PRA, ng angiotensin I/mL plasma/h, RIA) of 0.7. After the salt-depletion protocol PRA values taken 3 h after the furosemide dose have risen to about 7.4. Whereas blood pressure of normotensive rats that have not been salt-depleted does not change in response to treatment with the nonpeptide angiotensin receptor antagonist, DuP-753, salt-depleted animals typically respond with a blood pressure decrease of about 35 mmHg (mean arterial pressure, MAP). PRA is increased by this DuP-753 treatment to about 41.4.

[0090] Compounds that decrease blood pressure 10 or more mmHg (MAP) compared to concurrent control after oral dosing are considered active in this test. Maximum possible response is about -35 mmHg. Compounds that are not orally active are retested by giving a solution dose intra-arterially through the blood pressure cannula three hours after a furosemide dose.

Biological Activity:

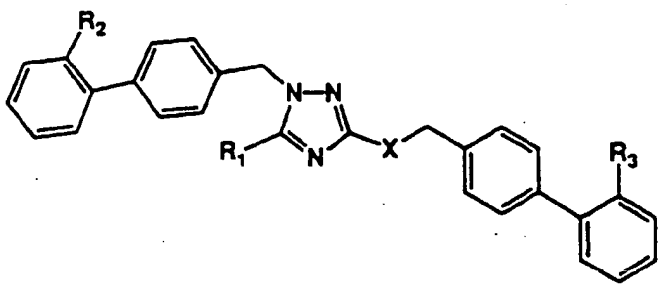
[0091]

Biological Activity:		
Compound	% Inhib. @ 10uM	pA2
2	100	8.49
4	100	7.49
6	100	8.39
8	100	7.96
9	2	-
10	97	6.73
12	79	
21	4	-
23	100	7.19
25	1	-
26	48	5.88
16		5.00
40	100	8.05
38	87	6.09
39	89	6.49

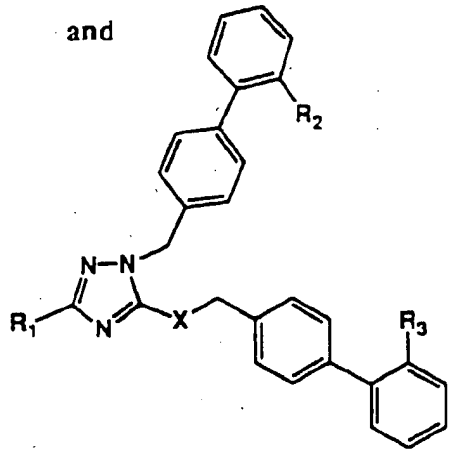
[0092] pA2 is the negative logarithm of the antagonist concentration that causes a 2-fold shift to the right (i.e. decrease) in the potency of the agonist or the negative logarithm of the antagonist concentration that cuts the potency of the agonist in half.

Claims

1. A compound of the formula



and



Wherein

R_1 is selected from H, C_{1-10} alkyl, C_{2-10} alkenyl, benzyl, phenylalkenyl, substituted benzyl wherein the substituent is selected from C_{1-6} alkyl, NO_2 and halo; phenyl and substituted phenyl wherein the substituent is selected from C_{1-6} alkyl, NO_2, C_{1-6} alkoxy and halo;

R_2 and R_3 are the same or different and are selected from CO_2H, CO_2C_{1-6} alkyl, CN, $CONH_2$, $CON(R_4)_2$ wherein R_4 is C_{1-6} alkyl; 5-tetrazolo, CONHOH and $CONR_4OH$, wherein R_4 is C_{1-6} alkyl; $CONHR_4$ wherein R_4 is 5-tetrazolo and X is selected from S, SO and SO_2.

2. The compound of claim 1 wherein R_1 is C_{1-10} alkyl; R_2 is COOH or 5-tetrazolo and R_3 is COOH, CN or COO_2C_{1-6} alkyl.

3. The compound of claim 1 or claim 2 wherein X is S.

4. The compound of claim 1 or claim 2 wherein X is SO.

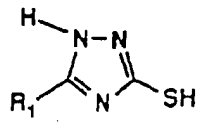
5. The compound of claim 1 or claim 2 wherein X is SO_2.

6. The compound of claim 1 selected from the group consisting of disodium 5-butyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole; 5-pentyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazole; 3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl). benzyl]-1,2,4-triazole; 3-[4-(2'-cyanophenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazole; and 1-[(2'-carboxyphenyl)benzyl]-3-[(2'-carboxyphenyl)benzylsulfonyl]-5-heptyl-1,2,4-triazole.

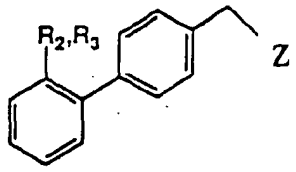
7. A pharmaceutical composition comprising an effective amount of a compound of any one of claims 1 to 6 as the active ingredient dispersed in a pharmaceutically acceptable carrier.

8. A compound of any one of claims 1 to 6 for use in treating a physiological condition in a mammal that is mediated by angiotensin II.

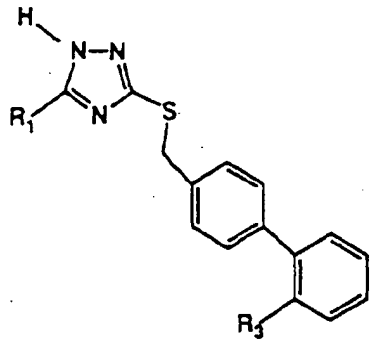
9. A process for preparing a compound of any one of claims 1 to 6,
which comprises reacting a substituted mercaptotriazole of the formula:



with a biphenylyl halide of the formula:

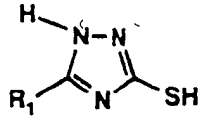


in the presence of one equivalent of a base to form a compound of the formula:

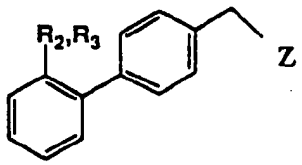


reacting the product formed with a second equivalent of of the base, and the same biphenylyl halide, and optionally oxidising the -S- group to an -SO- or -SO_2- group, wherein Z is selected from bromo and chloro.

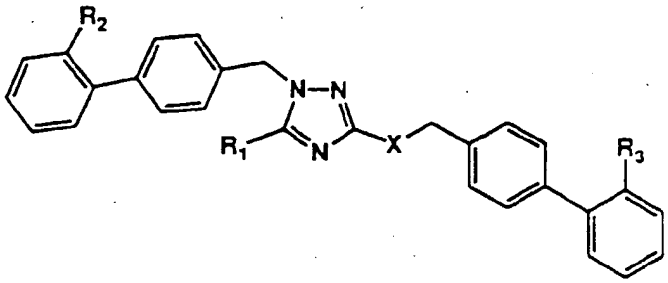
10. A process for preparing a compound of any one of claims 1 to 6, which comprises reacting one equivalent of a substituted mercaptotriazole of the formula:



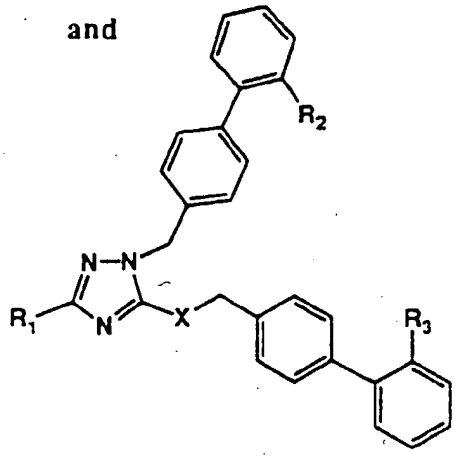
with two equivalents of a biphenylyl halide of the formula:



wherein R_2,R_3 is CO_2C_{1-6} alkyl or CN and Z is Cl, Br, or I,
in the presence of two equivalents of a base to form a mixture of compounds of the formula:



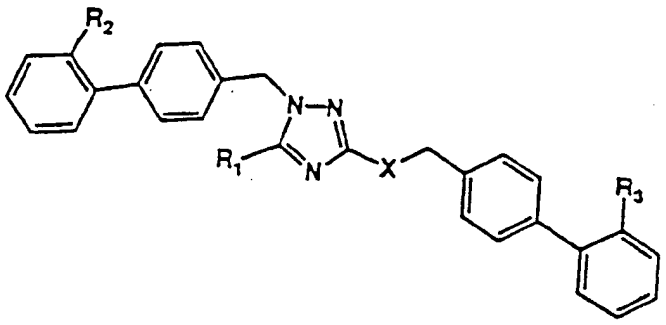
and



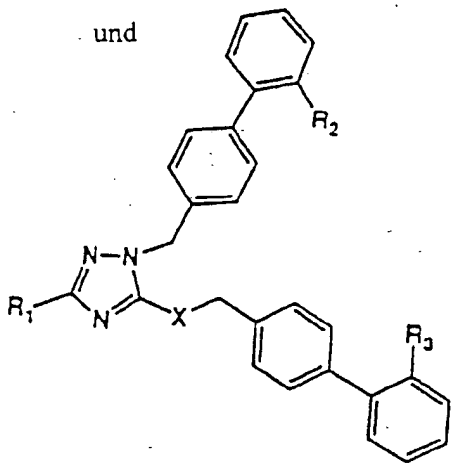
separating the products formed; and optionally oxidising the -S- group to an -SO- or $-SO_2-$ group.

Patentansprüche

1. Verbindung der Formel



und



bei der

R_1 unter H, C_{1-10}-Alkyl, C_{2-10}-Alkenyl, Benzyl, Phenylalkenyl, substituiertem Benzyl ausgewählt ist, wobei der Substituent unter C_{1-6}-Alkyl, NO_2 und Halogen ausgewählt ist; Phenyl und substituiertem Phenyl, wobei der Substituent unter C_{1-6}-Alkyl, NO_2, C_{1-6}-Alkoxy und Halogen ausgewählt ist;

R_2 und R_3 gleich oder verschieden sind und unter CO_2H, CO_2C_{1-6}-Alkyl, CN, $CONH_2$, $CON(R_4)_2$ ausgewählt sind, wobei R_4 C_{1-6}-Alkyl ist; 5-tetrazolo, CONHOH und $CONR_4OH$, wobei R_4 C_{1-6}-Alkyl ist; $CONHR_4$, wobei R_4 5-tetrazolo ist, und X unter S, SO und SO_2 ausgewählt ist.

2. Verbindung nach Anspruch 1, bei der R_1 ein C_{1-6}-Alkyl ist; R_2 eine COOH oder 5-Tetrazolo ist und R_3 eine COOH, CN oder COO_2C_{1-6}-Alkyl ist.

3. Verbindung nach Anspruch 1 oder 2, bei der X 5 beträgt.

4. Verbindung nach Anspruch 1 oder 2, bei der X SO ist.

5. Verbindung nach Anspruch 1 oder 2, bei der X SO_2 ist.

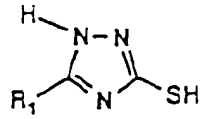
6. Verbindung nach Anspruch 1, die aus der Gruppe ausgewählt ist, die aus Dinatrium-5-butyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazol; 5-Pentyl-1,3-bis[4-(2'-carboxyphenyl)benzyl]mercapto-1,2,4-triazol; 3-[4-(2'-carbomethoxyphenyl)benzyl]mercapto-5-pentyl-1-[4-(2'-tetrazolophenyl)-benzyl]-1,2,4-triazol; 3-[4-(2'-cyanophenyl)benzyl],mercapto-5-pentyl-1-1[4-(2'-tetrazolophenyl)benzyl]-1,2,4-triazol und 1-[(2'-carboxyphenyl)benzyl]-3-<<[(2'-carboxyphenal)benzylsulfonyl]-5-heptyl- 1 ,2,4-triazol besteht.

7. Pharmazeutische Zusammensetzung, die eine wirksame Menge einer Verbindung nach einem der Ansprüche 1

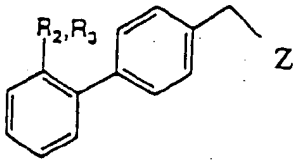
bis 6 als aktiven Inhaltsstoff in einer pharmazeutisch annehmbaren Trägersubstanz dispergiert enthält.

8. Verbindung nach einem der Ansprüche 1 bis 6 zur Verwendung bei der Behandlung eines physiologischen Zustandes in einem Säugetier, der durch Angiotensin II vermittelt wird.

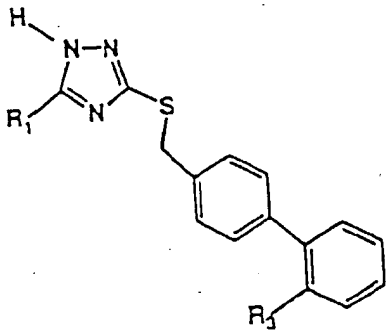
9. Verfahren zum Herstellen einer Verbindung nach einem der Ansprüche 1 bis 6, das das Umsetzen eines substituierten Mercaptotriazoles der Formel



mit einem Biphenylylhalid der Formel

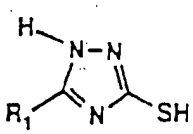


in Gegenwart eines Basenäquivalentes umfaßt, um eine Verbindung der Formel

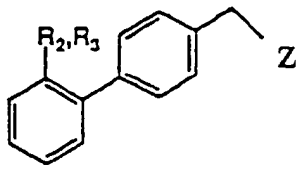


zu bilden und Umsetzen des gebildeten Produktes mit einem zweiten Basenäquivalent und dem gleichen Biphenylylhalid; und wahlweise Oxidieren der -S- -Gruppe in einer - SO- oder -SO_2- -Gruppe, bei der Z unter Brom oder Chlor ausgewählt ist.

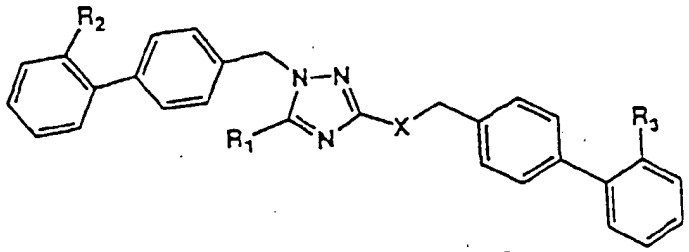
10. Verfahren zum Herstellen einer Verbindung nach einem der Ansprüche 1 bis 6, das das Umsetzen eines Äquivalentes eines substituierten Mercaptotriazoles der Formel



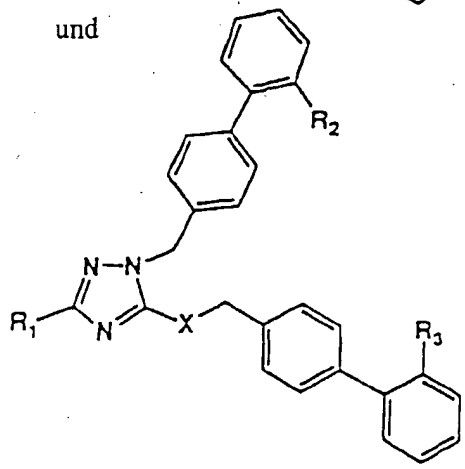
mit zwei Äquivalenten eines Biphenylylhalids der Formel



umfaßt, wobei R_2, R_3 ein CO_2C_{1-5}-Alkyl oder CN ist und Z ein Cl, Br oder I ist, in Gegenwart von zwei Basenäquivalenten umfaßt, um eine Mischung von Verbindungen der Formel



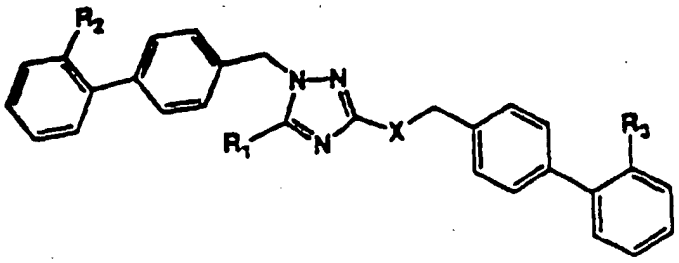
und



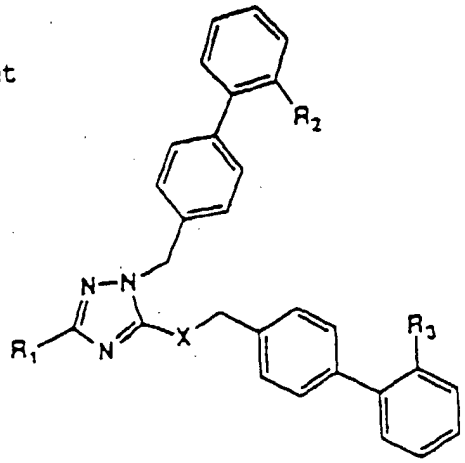
zu bilden, Trennen der gebildeten Produkte; und wahlweise Oxidieren der - S- -Gruppe in einer - SO- oder - SO_2- -Gruppe.

Revendications

1. ~~Composé de formule~~



et



où

R_1 est sélectionné parmi H, un alkyle en C_{1-10}, un alkényle en C_{2-10}, un benzyle, un phénylalkyle, un benzyle substitué où le substituant est sélectionné parmi un alkyle en C_{1-6}, NO_2 et un halo; un phényle et un phényle substitué où le substituant est sélectionné parmi un alkyle en C_{1-6}, NO_2, un alcoxy en C_{1-6} et un halo;
R_2 et R_3 sont identiques ou différents et sont sélectionnés parmi CO_2H, CO_2 alkyle en C_{1-6}, CN, $CONH_2$, $CON(R_4)_2$ où R_4 est un alkyle en C_{1-6}; un 5-tétrazolo, CONHOH et $CONR_4OH$, où R_4 est un alkyle en C_{1-6}; $CONHR_4$ où R_4 est un 5-tétrazolo et X est sélectionné parmi S, SO et SO_2.

2. Composé selon la revendication 1 où R_1 est un alkyle en C_{1-10}; R_2 est COOH ou un 5-tétrazolo et R_3 est COOH, CN ou COO_2 alkyle en C_{1-6}.

3. Composé selon la revendication 1 ou la revendication 2 où X est S.

4. Composé selon la revendication 1 ou la revendication 2 où X est SO.

5. Composé selon la revendication 1 ou la revendication 2 où X est SO_2.

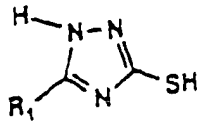
6. Composé selon la revendication 1 sélectionné dans le groupe consistant en le disodium 5-butyl-1,3-bis[4-(2'-carboxyphényl)benzyl]mercapto-1,2,4-triazole; le 5-pentyl-1,3-bis[4-(2'-carboxyphényl)benzyl]mercapto-1,2,4-triazole; le 3-[4-(2'-carbométhoxyphényl)benzyl]mercapto-5-pentyl-1-[4-(2'-tétrazolophényl)-benzyl]-1,2,4-triazole; le 3-[4-(2'-cyanophényl)benzyl]mercapto-5-pentyl-1-[4-(2'-tétrazolophényi)benzyl]-1,2,4-triazole, et le 1-[(2'-carboxyphényl)benzyl]-3-[(2'-carboxyphényl)benzylsulfonyl]-5-heptyl-1,2,4-triazole.

7. Composition pharmaceutique comprenant une quantité efficace d'un composé selon l'une quelconque des revendications 1 à 6 en tant qu'ingrédient actif dispersé dans un porteur pharmaceutiquement acceptable.

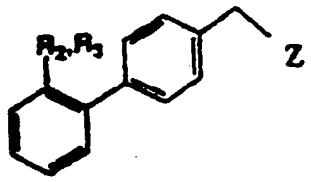
8. Composé selon l'une quelconque des revendications 1 à 6 pour utilisation dans le traitement d'un état physiologique

dans un mammifère qui est médiaté par l'angiotensine II.

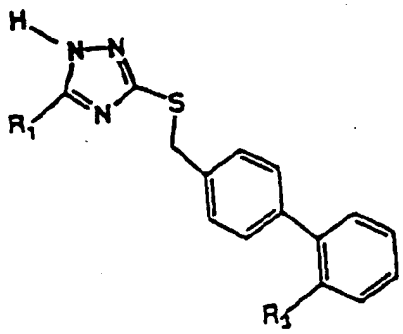
9. Procédé pour préparer un composé selon l'une quelconque des revendications 1 à 6, qui comprend la réaction d'un mercaptotriazole, substitué de formule:



avec un biphénylyl halogénure de formule:

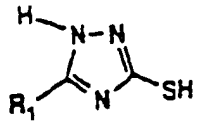


en présence d'un équivalent d'une base pour former un composé de formule:

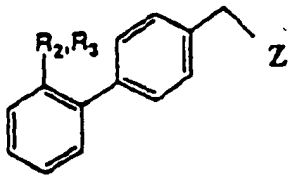


la réaction du produit formé avec un second équivalent de la base, et le même biphénylyl halogénure; et optionnellement l'oxydation du groupe -S- en un groupe -SO- ou $-SO_2-$, où Z est sélectionné parmi un bromo et un chloro.

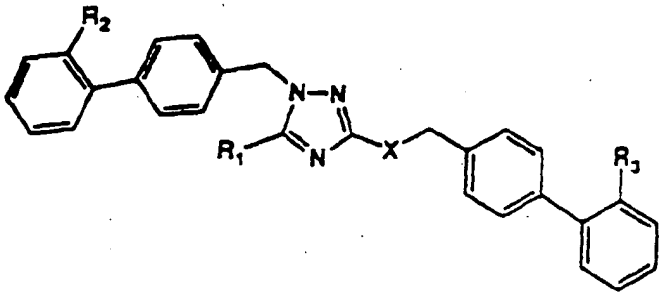
10. Procédé pour préparer un composé selon l'une quelconque des revendications 1 à 6, ~~qui comprend la réaction d'un équivalent d'un mercaptotriazole substitué de formule:~~



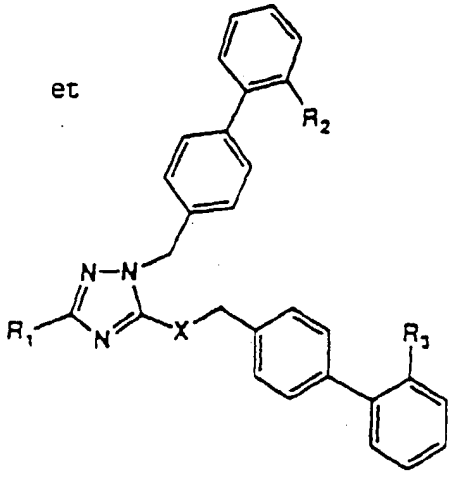
avec deux équivalents d'un biphénylyl halogénure de formule:



où R_2,R_3 est un CO_2 alkyle en C_{1-6} ou CN et Z est Cl, Br, ou I,
en présence de deux équivalents d'une base pour former un mélange des composés de formule:



et



la séparation des produits formés; et optionnellement l'oxydation du groupe -S- en un groupe -SO- ou $-SO_2-$.